STUDIES OF RANEY NICKEL - CATALYSED ASYMMETRIC HYDROGENATION REACTIONS.

BY

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To my Family

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SUMMARY

The hydrogenation of the prochiral β-keto ester, methyl acetoacetate, to the β-hydroxy ester, methyl 3-hydroxy butyrate, has been studied in some detail, using Raney nickel catalysts which have previously been treated with an optically active stereoisomer of tartaric acid. Various physical methods for the separation of the two enantiomers of the chiral reaction product have been investigated and the results are reported, together with a brief summary of recent developments in this field.

Variations in the reaction conditions and the methods of catalyst preparation and modification have been found to exert a considerable influence on the conversion and enantioselectivity obtained during reactions. As a consequence of carrying out extensive series of investigations, the conditions which result in maximum conversion and optimum enantiomeric excess have been identified. The catalyst with maximum enantio-differentiating ability is prepared by modifying Raney nickel with sodium bromide and optically pure tartaric acid at pH 3.2, with the temperatures of modification and Raney alloy alkaline digestion fixed at 100°C. Using a reaction temperature of 70°C and a minimum initial hydrogen pressure of 20 atmospheres, the liquid phase hydrogenation reaction should be carried out in the presence of the modified nickel catalyst with either butanol or methyl propionate as the solvent. Under these conditions, a conversion of 100% is obtained in conjunction

with an enantiomeric excess of magnitude 85%. This means that 92% of the chiral reaction product is in one enantiomeric form, while only 8% is in the other and so an extremely high enantioselectivity can be obtained.

In addition, certain conclusions regarding the mechanism of enantioselective hydrogenation are presented. Tartaric acid, present in the form of the monotartrate ion, $HC_4H_4O_6^-$, in the aqueous modifying solution, is assumed to be adsorbed on to the catalyst surface *via* its undissociated acid group and, by means of hydrogen bonding, behaves as a chiral "template" towards adsorbed substrate molecules. The enantioselective step, therefore, occurs before the addition of hydrogen to the adsorbed substrate. A possible explanation for the enhancing effect of the alkali halide sodium bromide is also provided.

CHAPTER ONE

INTRODUCTION

1.1 Historical Background of Optical Activity.

The precise origin of studies in optical activity and asymmetry in nature remains something of a mystery. However, as long ago as the early seventeeth century, the French philosopher René Descartes[1] recognised the existence of a lack of symmetry, perhaps in its most obvious form in man, when he remarked -

"Any man who, upon looking down at his bare feet, doesn't laugh, has either no sense of symmetry or no sense of humour"!

Undoubtedly, the discovery of polarised light marked a great advance in this subject. Following observations made by Bartholinus and Huygens[2] in the late seventeeth century, Malus,[3] in 1808, noticed that light became endowed with a special property when reflected from an opaque or transparent body. This property was that the vibrations of the light were all in one plane, which he called the "plane of polarisation" and thus the light itself was "polarised".

Several years later, in 1813, J.B. Biot[4] discovered that this plane of polarisation was rotated by quartz plate, cut at right angles to its crystal axis; in fact, some quartz crystals rotated the plane to the left while others rotated it to the right. In continuing these investigations, Biot later found that solutions of certain organic compounds, sugars, for example, also produced this plane rotating effect. He recognised that

there was a distinct difference between these two examples of "optically active species", where the term "optically active" described the ability to rotate plane polarised light:-

(i) The former was a property of the quartz crystal and depended on the direction from which the crystal was viewed.

(ii) In contrast, the latter was a property of individual, randomly arranged molecules, irrespective of whether in the gas or liquid phase or, alternatively, in solution.

During the next fifty years the special property exhibited by the quartz was attributed to the existence of hemihedral faces, the lack of symmetry of which resulted in a crystal being non-superimposable with its mirror image[5]. Thus, the idea of the occurrence of non-superimposable mirror images had been recognised.

However, it was not until 1860 that Louis Pasteur[6] extended this idea from the realm of crystals to that of molecules by attributing the optical activity of the latter to an asymmetric grouping of atoms within the molecules themselves. Thus, molecules of the same substance, which rotated the plane of polarisation of light to the left and right respectively, with the same magnitude, were related to each other as was an object to its mirror image. (Pasteur's contribution to this area of study was

immense, and a further aspect of his work will be discussed in a later section). The concepts of optical activity, caused by molecular asymmetry, and the tetravalent carbon atom, as described by Kekulé[7] in 1858, were eventually combined by van't Hoff[8] and Le Bel,[9] who, in 1874, introduced the tetrahedral carbon atom, shown in Figure 1.1.1:-

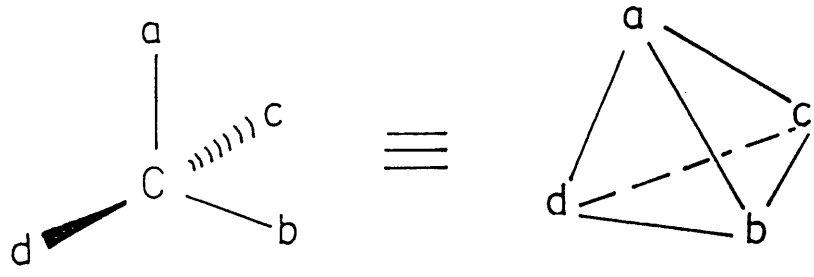
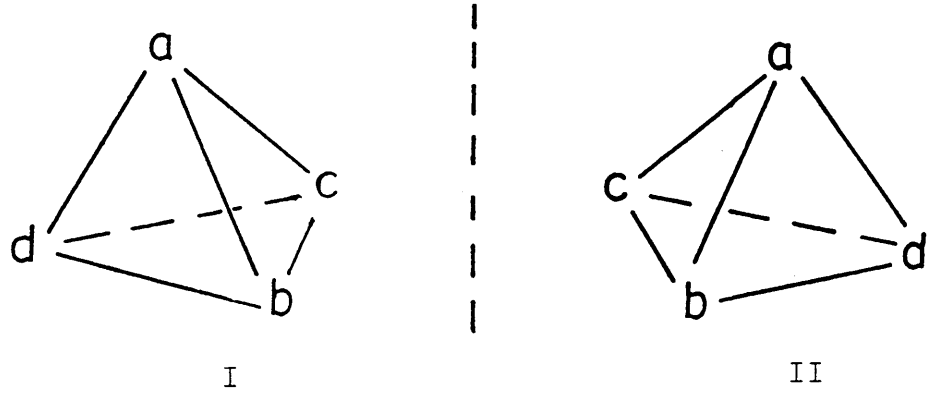


Figure 1.1.1

(a,b,c,d represent different groups).

The presence of the four, non-identical groups a,b,c,d led to the possibility of two structures for the species in Figure 1.1.1, which are shown in Figure 1.1.2; these structures are non-superimposable mirror images of each other:-



I II

Figure 1.1.2

If structure I rotated plane polarised light to the left, it followed that structure II would produce a rotation of equal magnitude to the right. The earliest nomenclature for optical rotation is shown in Table 1.1.1.

Table 1.1.1

Direction of rotation of plane polarised light.	Name
Right, +	Dextrorotatory, d
Left, -	Laevorotatory, l

Discoveries such as the fact that all sugars, for example, were dextrorotatory provided further evidence of optical activity in nature.

Despite the fact that the relationship between configuration and optical activity was now settled, there was, as yet, no proper understanding of how naturally occurring, optically active species were actually formed. The phenomenon remained a mystery, being explained in terms of an (unscientific!) concept, namely "vital force"[10]. This was still the case when, in 1894, Emil Fischer[11] began to study asymmetric reactions. He related his results (concerning the reaction of cyanohydrin with sugars) to the synthesis of optically active sugars in plant cells. In 1904, however, the first "scientific" theory as to the mechanism of asymmetric reactions was postulated by

Marckwald[12] and, in the next four decades, further mechanisms were put forward; in particular, Doering[13] and Jackman[14] proposed the existence of some intermediate while, later, Cram[15] and Prelog[16] produced empirical rules for asymmetric reduction, based on steric hindrance. Consequently, it had become possible to predict the outcome of asymmetric syntheses, thereby making it easier to obtain the desired product.

Before any detailed discussion of asymmetric synthesis can begin, however, it is necessary to define certain nomenclature and terms which will be involved.

1.2.1 Molecular Symmetry and Chirality.

Following the discovery that the requirement for molecular optical activity was that the molecule could exist in two, non-superimposable mirror image configurations, it was desired to find a simple method for determining whether or not this was the case; for example, the presence of asymmetric carbon atoms was neither a necessary nor sufficient condition for optical activity. The solution was found in the consideration of which symmetry elements were present in the molecule itself.

The symmetry elements and corresponding operations possible for finite bodies are shown in Table 1.2.1.1.

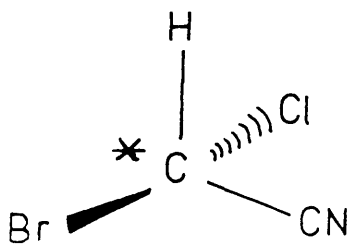
Table 1.2.1.1

Symmetry Element	Symmetry Operation	Symbol
Rotation axis of order n	Rotation around axis by $\frac{2\pi}{n}$ radians	C_n
Alternating axis of order n	Rotation around axis by $\frac{2\pi}{n}$ radians, followed by reflection in plane perpendicular to axis	S_n
Plane of symmetry	Reflection in plane	σ
Centre of symmetry	Inversion through centre of symmetry	i

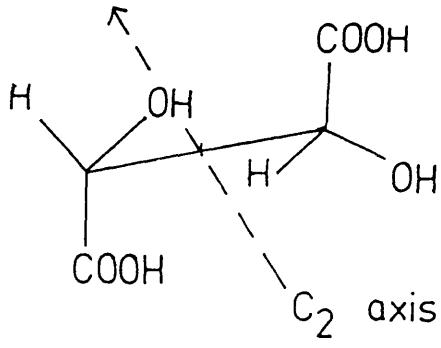
The term "asymmetric" was given to molecules containing no symmetry elements other than C_1; however this was not a necessary condition for optical activity. It was in fact found that the absence of an alternating axis of any order was equivalent to the property of non-superimposable mirror image configurations, and the term given to such molecules was "dissymmetric". Thus, the necessary and sufficient condition for optical activity was that a molecule should be dissymmetric. Examples of asymmetric and dissymmetric molecules are shown in Figure 1.2.1.2.

(a) ASYMMETRIC MOLECULE:- Chlorobromonitrile.

No.asymmetric C atoms	Point Group
1	C_1



(b) DISSYMMETRIC MOLECULE:- Optically Active Tartaric Acid (one conformational isomer)



No. Asymmetric C atoms	Point Group
2	C_2

Figure 1.2.1.2

However, the terms "asymmetric" and "dissymmetric" have essentially the same meaning, in that they are the opposites of "symmetric". In order to avoid confusion (especially since the term "non-dissymmetric" had to be introduced!) Cahn, Ingold and Prelog[17] suggested that the term "chiral" (based on the Greek word "cheiro", meaning "hand") should be applied to molecules which, either being asymmetric or dissymmetric, were optically active. The two, mirror image, configurations of the molecule were called enantiomers. (The use of the word "chiral" was not new - it had in fact been used in the same connection by Lord Kelvin[18] in 1904).

The opposite of the term "chiral" is "achiral", which is equivalent to the term "non-dissymmetric" - that is, achiral molecules contain an alternating axis of symmetry. There are many achiral molecules which can

be converted to chiral molecules by a single operation, such as replacement of one substituent with a different one, or the addition of a further substituent through some kind of reaction. Consider, for example, the planar molecule acetaldehyde, in which the central carbon is sp^2 bonded:-

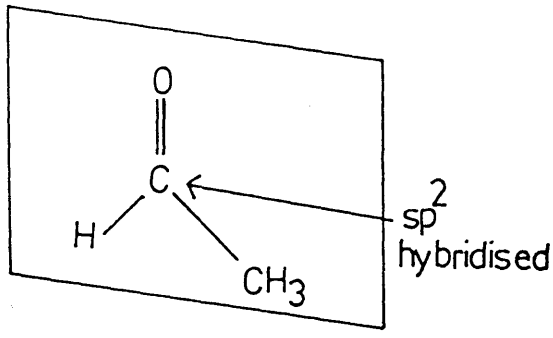


Figure 1.2.1.3

The molecule itself can be regarded as a plane of symmetry. Thus, if a fourth substituent were added, a chiral molecule will be produced. Such a topological property is termed prochirality (or, in particular sp^2 - prochirality) and a carbon atom of this type is referred to as a prochiral, or sp^2- prochiral centre.

1.2.2 Nomenclature for Absolute Configuration.

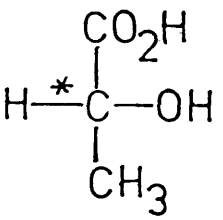
Three systems have been introduced for the purpose of defining configurations of chiral molecules.

(i) The (+), (-) System

This, the earliest system which was used, has

already been described in Section 1.1; the configuration of a particular stereoisomer of a compound was labelled "(+), dextrorotatory" or "(-), laevorotatory" depending on its effect on plane polarised light. For example, lactic acid, shown in Figure 1.2.2.1.

Figure 1.2.2.1



occurs naturally in both enantiomeric forms:-

(a) "Sacrolactic acid" (produced in muscle):- (+), dextrorotatory.

(b) "Fermentation lactic acid" (produced from fermentation of lactose during the souring of milk):- (-), laevorotatory.

This description is applicable to any chiral molecule.

(ii) The D, L System[19]

This system was introduced for the purpose of describing molecules of the type $R\overset{*}{C}HXR'$, where R - C - R' constitutes the main chain of the molecule according to the IUC convention.† It is based on Fischer projections of molecules and an example of how the system is used is shown in Figure 1.2.2.2; lactic acid is again the example of the chiral molecule.

†Most highly oxidised C atom takes priority, therefore, for example, CO_2H > CHO > CH_2OH

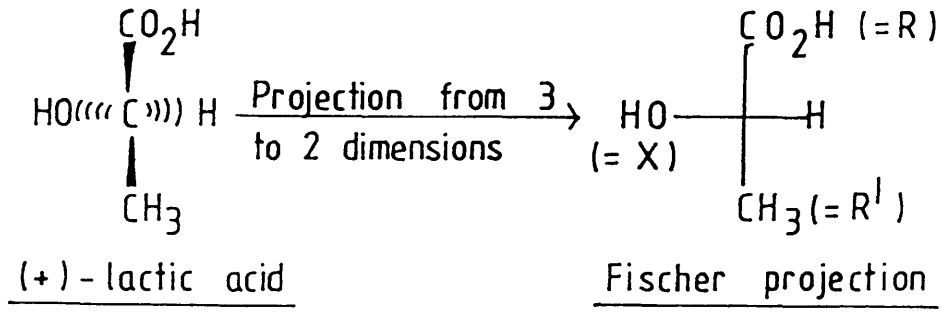


Figure 1.2.2.2

Thus, in the Fischer projection, the molecule is oriented so that the most highly oxidised carbon atom is at the top, and the main chain is vertical. Since, in the resulting Fischer projection, X(=OH) is on the left, the above structure would be that of (L)-(+)-lactic acid; if X had been on the right, the acid would have been (D)-(-)-lactic acid.

This system, however, is not suitable for molecules with more than one chiral centre in that, very often, such molecules could be labelled either (D) or (L) depending on how the molecule is viewed. Consequently, another system was suggested.

(iii) The (R),(S) Sequence Rule.

The alternative was found in the (R),(S) Sequence Rule, which was put forward by Cahn, Ingold and Prelog.[20] To avoid confusion with the (D),(L) system, new symbols were used, based on the latin words

(a) Rectus (right) - abbreviated to (R)

(b) Sinister (left) - abbreviated to (S)

Based on three-dimensional structures, as opposed to two-dimensional Fischer projections, this system avoided the ambiguities which arose when applying the (D), (L) system to molecules with more than one chiral centre. For molecules with tetrahedrally surrounded asymmetric atoms, the rules are -

(a) arrange 4 substituents in order of decreasing priority; for example, in the molecule *Xabcd, assume that a>b>c>d.

Then

(b) view the molecule from the side remote from d

(c) If the resulting picture is as shown in Figure 1.2.2.3,

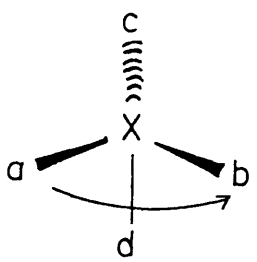


Figure 1.2.2.3

that is, a→b→c traces a COUNTER-CLOCKWISE turn, then the structure is labelled "S".

If the resulting picture is as shown in Figure 1.2.2.4,

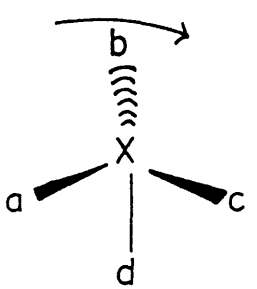


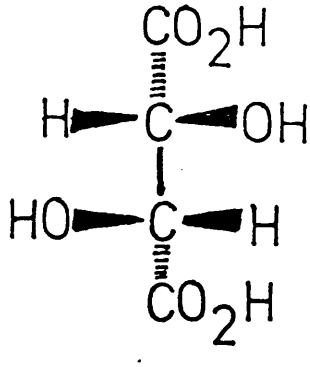
Figure 1.2.2.4

that is, a→b→c traces a CLOCKWISE turn, then the structure is labelled "R".

The groups a,b,c,d are arranged in order of decreasing atomic number of the atom directly attached to

the asymmetric atom; if two (or more) are identical, their respective states of substitution are considered in a similar manner.

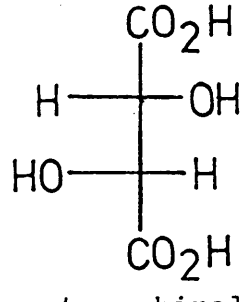
The advantage for molecules with two asymmetric atoms is that an (R) or (S) symbol is attached to each, thus removing any ambiguity. An example is shown in Figure 1.2.2.5



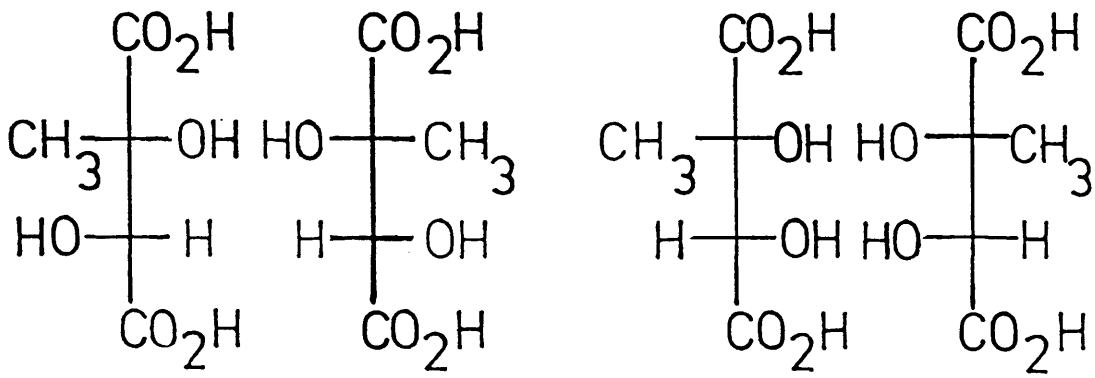
The configuration at both ^{2}C and ^{3}C is (R).

Figure 1.2.2.5

Hence this structure is described as (R,R)-(+)-tartaric acid. The corresponding Fischer projection is



Molecules containing two chiral centres can, in principle, exist in four configurationally isomeric structures; these four stereoisomers are shown in Figure 1.2.2.6 for tartaric acid.

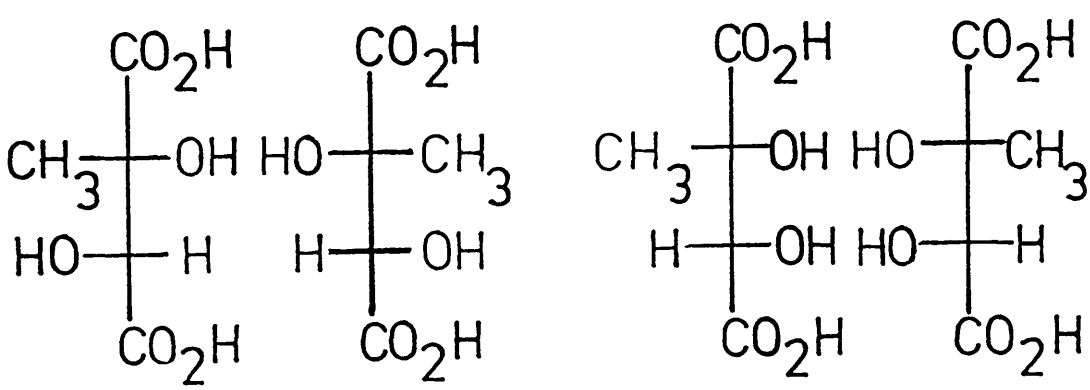


I (2R,3R)-(+) II (2S,3S)-(-) III (2S,3R) IV (2R, 3S)

Figure 1.2.2.6

However, since the two chiral centres are identical structures III and IV are identical and so, together, constitute the optically inactive Meso form, while the optically active structures I and II are enantiomeric.

In the case of a molecule containing two, non-identical chiral centres, all configurations are optically active. Figure 1.2.2.7 shows all possible structures of 2-methyl tartaric acid; two pairs of enantiomers, named threo and erythro respectively, exist.



I (2R,3R) II (2S,3S) III (2R,3S) IV (2S,3R)

(+) & (-) THREO (+) & (-) ERYTHRO

Figure 1.2.2.7

1.3 Asymmetric Synthesis

1.3.1 Definitions of Asymmetric Syntheses

An asymmetric reaction is classed as either enantioselective or diastereoselective, depending on the nature of the substrate involved.

An enantioselective synthesis involves the creation of a chiral product from a substrate which, although achiral, possesses a centre of prochirality. An example of such a reaction is the hydrogenation of butan-2-one, which is shown in detail in Figure 1.3.1.1.

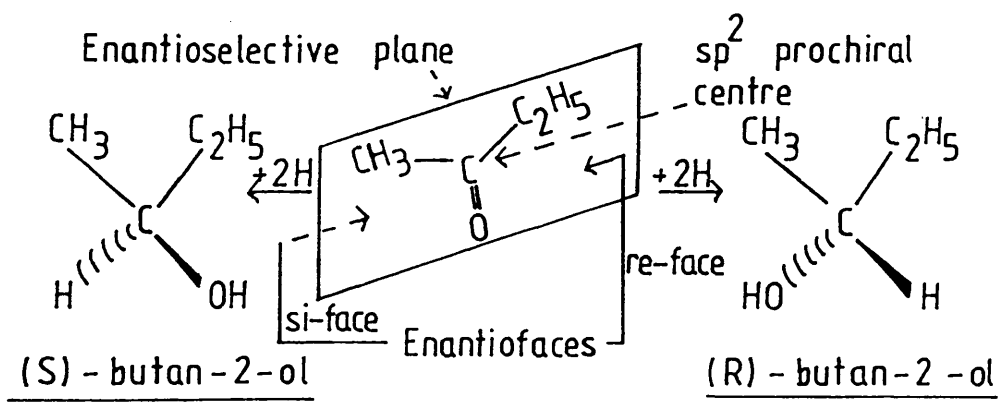


Figure 1.3.1.1.

The molecular plane is called the enantioselective plane and its two opposite faces called re- and si- enantiofaces respectively. In principle, both faces can be approached by the attacking hydrogen; if attack occurs from the side of the re- face, the alcohol molecule produced will be of (R)-configuration and, in contrast, (S)-alcohol will result from hydrogen attacking from the side of the si-face.

If unequal amounts of enantiomeric alcohols were obtained on hydrogenation of the ketone, it follows that some kind of differentiation between the two enantiofaces has taken place - that is, an enantioselective reaction has occurred. In order to achieve enantioselectivity, an asymmetric catalyst is normally required. In contrast, diastereoselective reactions involve the formation of a second chiral centre of preferred orientation due to the influence of a chiral centre initially present in the substrate. Thus, the reaction products are diastereomers, which are produced in unequal proportions. An example of a diastereoselective reaction is shown in Figure 1.3.1.2.

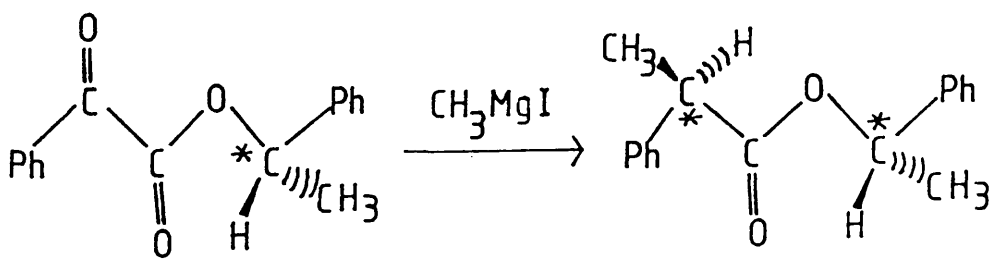


Figure 1.3.1.2.

There is however, no requirement for any asymmetric catalyst in order to perform a diastereoselective reaction.

1.3.2 The Requirement for Asymmetric Synthesis

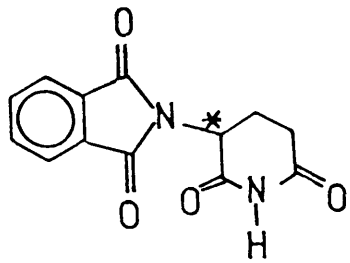
The fact that chirality is a fundamental feature in nature is now well established and various theories to account for its origin have been proposed.[21] For example, all naturally occurring sugars exist in the (D) form only,

while, in contrast, all naturally occurring amino acids exist in the (L) form - this means that proteins are composed of amino acids of one configuration only, a fact which influences the structure adopted by the protein itself.

It is now known that naturally occurring catalysts called enzymes ensure that, in a reaction which converts a prochiral substance into a chiral substance, only one enantiomer of the product is obtained. Thus, the presence of the enzyme results in both a product selectivity and enantioselectivity of 100%.

As a consequence of the chirality in biological systems, any added chemical will have an effect which is dependent both on its molecular composition and configuration. Thus, different enantiomers of the same compound can have largely different effects;while one may be extremely efficient in a chemical process the other may be completely ineffective or, alternatively, toxic. This obviously is a fact of crucial importance in, for example, the pharmaceutical industry during the synthesis of potential drugs. Care must be taken to ensure that only the enantiomer which will have a desirable effect is present in the final product in case the other were toxic. However, conventional synthetic methods result in a racemic mixture of chiral product, since the enantiomers are chemically identical; for the same reason, however, physical separation of enantiomers is generally a difficult and expensive process. An unfortunate outcome of administering a drug in racemic

form was evident in the case of thalidomide,



which was prescribed to expectant mothers in the late 1950's. While the (R)-(+)-form achieved the desired effect, the (S)-(-) form was metabolised into products which caused the infants subsequently born to have suffered severe physical handicap.

Consequently, asymmetric synthesis by means of some highly enantioselective catalyst is a very attractive technique. However, the use of enzymes in laboratory or industrial preparations is impractical for various reasons, in particular for hydrogenation and dehydrogenation reactions, and so some other asymmetric catalyst is required.

1.3.3 Measures of Asymmetric Synthesis

Regardless of the precise manner in which an asymmetric synthesis is carried out, it is conventional to quote results in terms of the "enantiomeric excess" which is obtained, as a measure of the degree to which enantioselectivity has occurred.

Consider the general reaction

$$A \longrightarrow (R)\text{- \& } (S)\text{- } {}^{*}B$$

where A is prochiral and *B is the chiral product. The "enantiomeric excess", denoted by e.e., is defined as

$$e.e. = \frac{c_R - c_S}{c_R + c_S} \times 100\% \qquad (1.3.3.1)$$

where c_R = concentration of (R)-*B produced

c_S = concentration of (S)-*B produced

The sign of the e.e. is dependent on which enantiomer has been produced in excess. If, for example, the reaction had failed to produce any (S)-*B, that is $c_S = 0$, it follows that the value of the e.e had reached a maximum of 100% in favour of the (R)-enantiomer. In contrast, if a racemic mixture of *B was produced, that is $c_R = c_S$, it follows that the e.e. had reached its minimum value of 0.

An alternative description of the enantioselectivity which has occurred is the "optical yield" obtained. The optical yield is defined as

$$\text{optical yield} = (c_R - c_S) \times 100\% \qquad (1.3.3.2)$$

Thus, optical yields are always greater than corresponding enantiomeric excesses, with the exception of when either a racemic mixture or pure enantiomer is obtained, in which cases both have values of 0 and 100% respectively.

There are normally two types of catalysts available for the purpose of asymmetric synthesis - homogeneous and heterogeneous.

1.4 Asymmetric Homogeneous Catalysts.

The first attempts to achieve chiral synthesis by means of the asymmetric hydrogenation of olefins had used heterogeneous catalysts for this purpose.[22] However, by the mid-1960's, it had become clear that these catalysts were incapable of interacting with olefins in a manner which would produce chiral compounds with high enantiomeric excesses.[23] Thus, these efforts were abandoned, but, at the end of the decade, a new approach was emerging as a result of two, independent occurrences:-

(i) Wilkinson's discovery[24] that alkenes were hydrogenated homogeneously with a rhodium-triphenylphosphine complex under very mild conditions.

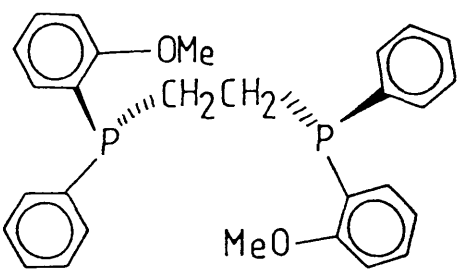
(ii) Mislow's development[25] of a preparative method which made possible the synthesis of a wide range of chiral phosphines.

These discoveries, coupled with a need to produce optically pure amino acids at a reasonable cost, led to a revitalization of interest in asymmetric hydrogenation using chiral rhodium-phosphine complexes as the catalysts.

1.4.1 Chiral Phosphine Ligands.

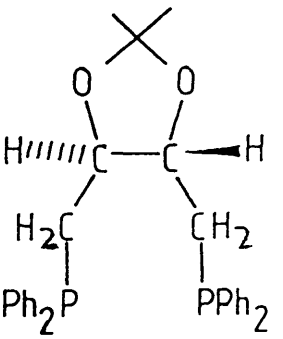
The use of rhodium complex catalysts with monodentate chiral phosphine ligands generally resulted in low optical yields.[26] However, superior results were obtained using chiral diphosphine ligands.[27] The chiral centre

could either be the coordinating phosphorus atom or, more commonly, in the carbon backbone connecting the two phosphine groups; an example of each type is shown in Figures 1.4.1.1. (a) and (b) respectively.



(R,R) - DIPAMP

(a)

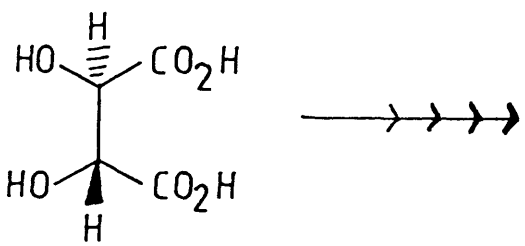


(R,R) - DIOP

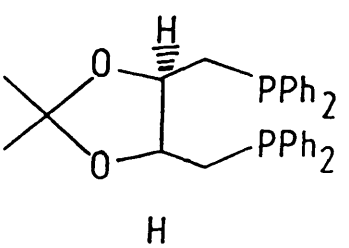
(b)

Figure 1.4.1.1.

It is perhaps interesting to note at this point that a suitable starting material for the synthesis of many chiral diphosphine ligands is (R,R)-(+)-tartaric acid,[28] for example:-



(R,R) - Tartaric acid
(naturally occurring)



(R,R) - DIOP

Irrespective of which particular diphosphine ligand is used, the catalytic diphosphine rhodium complex consists of a chiral array of four phenyl rings around one rhodium

atom, which is the chiral "template" responsible for enantioselective hydrogenation,[29] shown in Figure 1.4.1.2

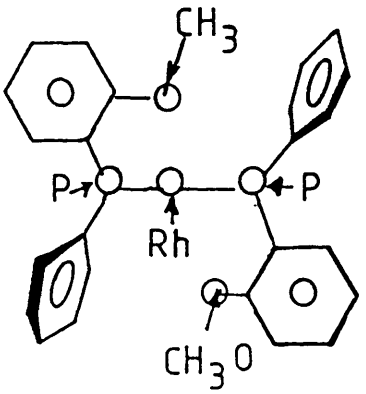
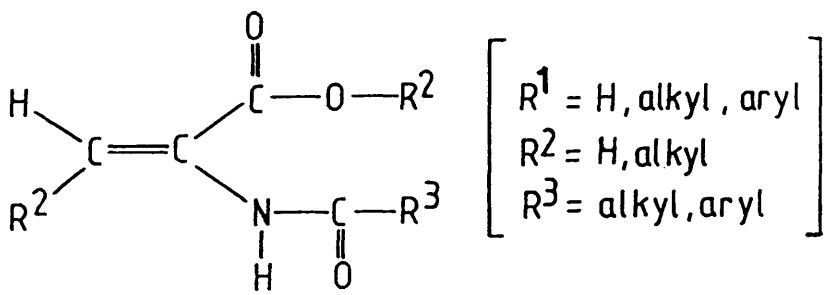


Figure 1.4.1.2.

1.4.2 Substrates in Asymmetric Hydrogenation.

The highest optical yields using the catalysts described in Section 1.4.1 were obtained on the hydrogenation of α-aminocinnamic or acrylic acids or esters[30]; the general structure is



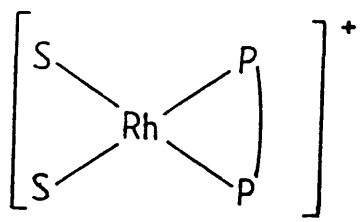
Z - isomer

It was generally found that the (Z)-isomers of these compounds were hydrogenated more rapidly and with higher optical yields than the corresponding (E)-isomers. This structure allows the substrate to chelate to the rhodium complex catalyst.

1.4.3 The Mechanism of Asymmetric Hydrogenation[31]

With the aid of techniques such as ^{1}H, ^{13}C and ^{31}P nmr spectroscopy, the mechanism of asymmetric hydrogenation is now well understood.

The catalyst precursor has an ionic, square planar structure and is usually a diene adduct. This adduct is activated to form the true catalyst, which is a solvated complex and so can be represented as



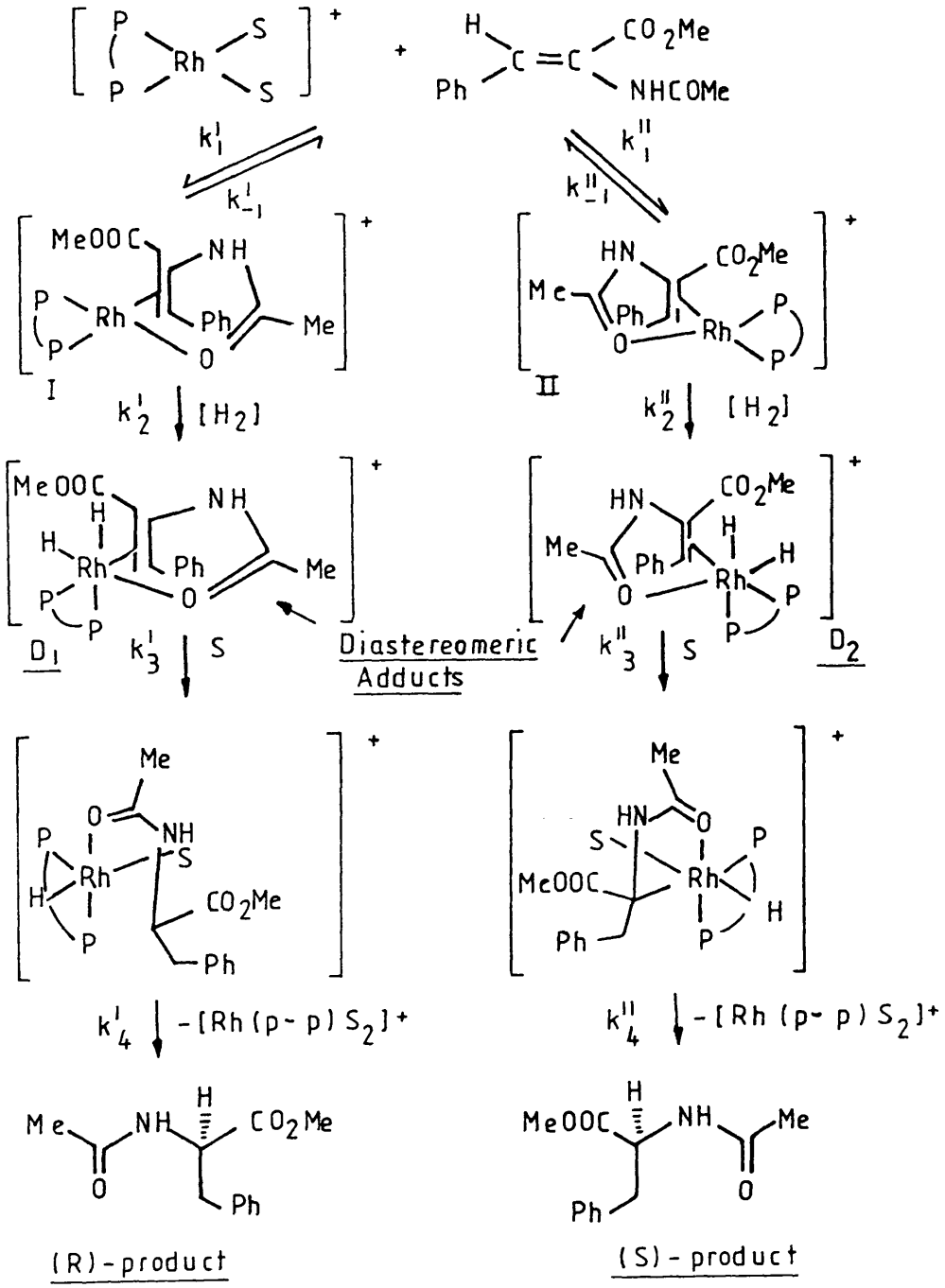
where S = solvent molecule

$\overset{\frown}{P\ P}$ = chiral diphosphine ligand.

Figure 1.4.3.1 is an illustration of the mechanism of asymmetric hydrogenation.

Since one mode of binding of substrate to catalyst will be more favourable than the other, as a result of the ability of the chiral array of phenyl rings to differentiate between the two enantiofaces of the substrate, the two complexes I and II will be formed in different amounts. Consequently, the diastereomeric adducts D_1 and D_2 are also formed in different amounts. It is perhaps unexpected that the predominant enantiomer of the product arises from the minor and not the major diastereomer, as a result of the former being much more

Figure 1.4.3.1 The Mechanism of Asymmetric Hydrogenation



reactive than the latter; in fact, this difference in reactivity $\frac{(k'_2)}{k''_2}$ must be in the region of 10^3 to afford the enantiomeric excesses of over 95% which are frequently obtained. In the case of using the ligand (R,R)-DIPAMP in Figure 1.4.3.1, the (S)-product is obtained with an enantiomeric excess of 96%. Therefore, the stable "unproductive" adduct must be D_1 while the highly reactive, minor adduct must have been D_2.

To summarise, it must be said that tremendous success has been achieved in the homogeneously catalysed asymmetric hydrogenation of olefins. As a result, compounds which can easily be transformed into amino acids can be obtained with excellent enantioselectivities.

Perhaps one of the most famous examples has been the synthesis of (L)-3,4-dioxyphenylanine, (L)-DOPA[32] which has proved to be very successful in the treatment of Parkinson's Disease.

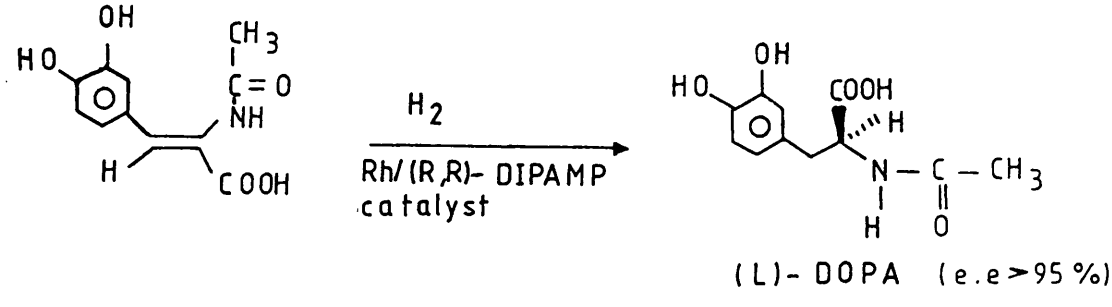
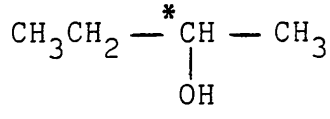


Figure 1.4.3.2.

However, regardless of how excellent these homogeneous catalysts may be, there will always remain the problem of recovering the catalyst from the product mixture at the end of a reaction. Added to this, there is the inescapable fact that the catalysts are highly expensive to produce. For commercial purposes, therefore, it would always be desirable to replace homogeneous with heterogeneous catalysts in order to avoid the problem of catalyst recovery and also to lessen the cost. In the light of this, it seems unlikely that any search for suitable asymmetric heterogeneous catalysts will be completely in vain.

1.5 The Discovery of Asymmetric Heterogeneous Catalysts.

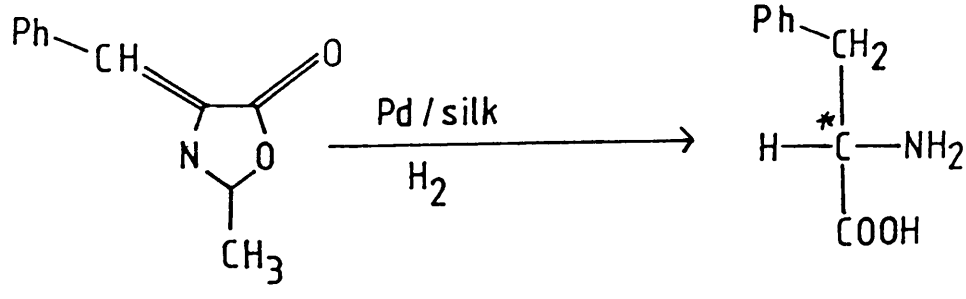
The first reports of asymmetric heterogeneous catalysts appeared in the early 1930's, following Schwab's observations using unimolecular deposits of copper, platinum[33] and nickel[34] on the dextrorotatory and laevorotatory faces of quartz. Schwab had noticed that, after dehydrating racemic butan-2-ol,



on laevorotatory quartz, the remaining alcohol was then laevorotatory. In contrast, the remaining alcohol became dextrorotatory following the oxidation in air of a racemic mixture; these two effects were observed irrespective of which metal was present and the reverse results obtained when the experiments were performed on

dextrorotatory quartz. Unfortunately, it was not possible to carry out any asymmetric hydrogenation reactions, owing to the much greater thickness of metal deposit required to effect hydrogenation.

There was no further report on this subject for over twenty years; however, in 1956, Akabori[22] published his discovery that small optical yields were obtained on the hydrogenation of C=C and C=N bonds in the presence of an optically active palladium catalyst. This catalyst had been prepared from palladium chloride previously absorbed on an optically active support of silk fibroin, that is, the water-insoluble structural protein from silk. An example from his work is the reaction shown in Figure 1.5.1.



4-benzylidene-2-methyl-oxazol-5-one, I

phenylalanine, II (excess of (R)- obtained)

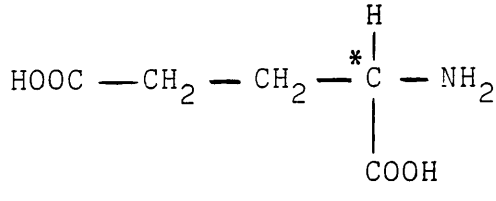
Figure 1.5.1

The optical yields obtained in Akabori's work were, however, generally low and irreproducible.

Studies on the silk fibroin system were continued

by Izumi using palladium,[35] platinum[36] and rhodium[37] metals in the hydrogenation of various C=C, C=O and C-NO_2 bonds. Although interesting selectivity effects were observed, there was a complete lack of optical activity in the chiral products obtained. Consequently, attempts to develop the silk fibroin system for use in asymmetric heterogeneously catalysed reactions were abandoned. Despite this lack of success, however, the idea of using a metal catalyst in conjunction with some optically active material, or "modifier", as it became known, was born.

Since the silk-metal catalyst had very little hydrogenation activity in the reduction of carbonyl compounds to alcohols, it was concluded that the catalyst specificity was introduced by the structure of the carrier protein, that is, peptide bonds, amino groups and carbonyl groups. If it were true that the functional groups containing lone pairs were bound more firmly to active centres, the hydrogenation activity of the catalyst with respect to carbonyl groups would diminish, thus inducing a specificity on the catalyst. Strong selectivity effects were also observed when compounds containing various C=C and C=O bonds were hydrogenated in the presence of a Raney nickel catalyst which had been treated with (L)-glutamic acid,



that is, the activity of the catalyst for C=C hydrogenation

was unaffected while that for C=O hydrogenation was greatly diminished.[38] Thus, the α-amino acid had the same effect on the catalytic behaviour of the metal as the more complex, polypeptide protein.

However, Isoda[39] had also observed that, in the presence of a Raney nickel catalyst modified with an amino acid, small optical yields were obtained on the hydrogenation of various carbonyl compounds. Consequently, the heterogeneous catalytic system, which had previously failed to achieve the asymmetric hydrogenation of olefins, was once again under investigation.

Before any further details of asymmetrically modified Raney nickel catalysts are described, a brief summary of the general properties of Raney nickel is presented.

1.6 Raney Nickel

1.6.1 The Preparation, Composition and Structure of Raney Nickel.

In 1925, Murray Raney announced a novel preparation of a highly active nickel catalyst[40] and it transpired that this report was to be the origin of a completely new type of catalyst. In recognition of Murray Raney's efforts, these catalysts were named Raney catalysts and the factor common to all was the method of preparation, which involved the use of some binary alloy as the starting material.

Thus, Raney nickel is formed by the following process:-

$$\text{Ni:Al alloy} \xrightarrow{\text{aqueous sodium hydroxide}} \text{Pyrophoric Raney Nickel}$$

During the leaching of the nickel:aluminium alloy with alkali, a large part of the aluminium is removed as water-soluble sodium aluminate and the Raney nickel catalyst which remains has a porous, skeletal structure with a high surface area. This structure is perhaps best described as an aggregate of crystallites, ranging from 25 to 100Å in diameter, which are held together in the shape of a sponge, while the average pore radius is about 34Å.[41]

Raney nickel generally consists mainly of nickel with a small amount of nickel oxide, some residual aluminium (1-8%) and, lastly, alumina (1-20%), most of which is thought to be hydrated. The total nickel surface area amounts to 70-80% of the total metallic surface area, normally in the region of 50-130 $m^2 g^{-1}$, and so there must be some surface aluminium present to account for the remaining 20-30%.[41,42]

X-ray diffraction experiments have shown that the structure of the nickel metal has that of a face centred cubic lattice[43]; since the lattice constant obtained for Raney nickel (3.53Å) differed only slightly from that obtained for pure nickel (3.525Å), the authors attributed the deviation to the presence of small amounts of aluminium,

most of which was dissolved in the nickel lattice.

Raney alloy generally consists of a mixture of several phases : $NiAl_3$, Ni_2Al_3 and NiAl in proportions correlated to the Ni/Al ratio. These different phases do not have the same reactivity to alkaline solutions.[44] It follows that, according to the starting alloy and to the leaching conditions, different Raney nickel catalysts are obtained, which may vary in the proportion and localisation of residual aluminium and in the possible presence of metallic oxides. For this reason, there will be a variation in, for example, surface area and crystallite size between Raney catalysts; such differences have been confirmed by Damon[45] by means of investigations using $NiAl_3$ and Ni_2Al_3 single and dual phase alloys. Furthermore, differences in catalyst activity as a result of varying the phase composition of the original alloy have also been reported,[46,47] although no such differences had been found by Damon, who studied the Raney nickel catalysed hydrogenation reactions of benzene and isoprene.

A further aspect of the composition of Raney nickel is its substantial hydrogen content, most of which is removable on heating. There have been extensive investigations using a variety of techniques, which have endeavoured to determine the exact quantity of hydrogen contained, as well as its location within the catalyst structure, and these will now be discussed in some detail.

1.6.2 The Hydrogen Content of Raney Nickel.

Quantitative measurements of the amount of hydrogen contained in Raney nickel catalysts can be made by three different methods:-[43]

(i) Measuring the change in weight of the catalyst sample, or

(ii) Following volumetrically the amount of gas produced, as hydrogen is evolved on heating

(iii) Monitoring the extent of hydrogenation of organic compounds using Raney nickel in the absence of any additional hydrogen gas.

There is considerable variation in the results which have been reported, but hydrogen contents of around $100cm^3/(gNi)$ appear to be the most common.

For the purpose of investigating the nature of the hydrogen content, magnetic measurements have proved to be extremely useful.[48] Unfortunately, however, great controversy exists over the interpretation of results obtained from magnetic measurements. There have in fact been five basic proposals for the hydrogen contained in Raney nickel:-

(i) a 3-dimensional hydride, NiH_2, is present,[40,49]

(ii) Hydrogen is dissolved in the bulk metal or interstices (that is, there is a substitutional replacement of nickel atoms in the lattice.[50])

(iii) Hydrogen is generated by the reaction of nickel or aluminium with water.[43]

(iv) There is a solid solution of hydrogen in nickel[51]

(v) Hydrogen is chemisorbed on nickel atoms[52]

Mars' group[43] have in fact postulated that there were no less than three sources of hydrogen:-

(a) chemisorbed hydrogen ($27cm^3/(gNi)$)

(b) Hydrogen produced by the reaction of aluminium with hydrated alumina:-

$$Al(OH)_3 + Al \longrightarrow Al_2O_3 + {}^3/_2H_2 \qquad (23cm^3/(gNi))$$

(c) Hydrogen produced from the reaction of adhering water with aluminium, the amount of which was variable.

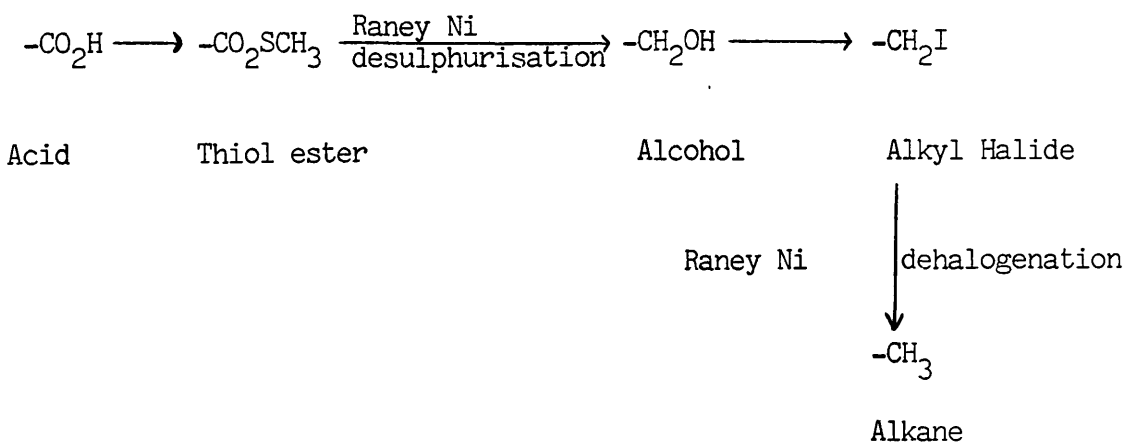
In an effort to settle this controversy, Martin and Fouilloux[53] carried out magnetic studies on Raney nickel catalysts free from any alumina. Their results were not consistent with the theory that aluminium was reacting with adhering water to produce hydrogen, on the contrary, the magnetic, surface area and catalytic activity data were best interpreted by assuming that hydrogen was mainly present as a chemisorbed gas. Despite the apparently conclusive evidence for this, however, the fact remained that these experiments had used alumina-free catalysts and so a comparison of the results with those obtained from studies of catalysts containing alumina was not strictly valid.

Therefore, the nature of hydrogen contained in Raney nickel remains unclear. Perhaps the only firm conclusion which can be made is that the true state of the catalyst is a combination of two or more of the five

possibilities previously mentioned in this Section.

1.6.3 Uses of Raney Nickel

In spite of the fact that there are aspects of the structure and composition of Raney nickel which are yet to be fully understood, its versatility and effectiveness as a catalyst result in it being used in a wide variety of chemical reactions. Hydrogenation, dehydrogenation, desulphurisation and disproportionation reactions represent some of the processes catalysed by Raney nickel and, consequently, the catalyst is often employed in organic synthesis; for example, in the conversion of a $-CO_2H$ group to $-CH_3$, Raney nickel is used in two out of a total of four steps:-

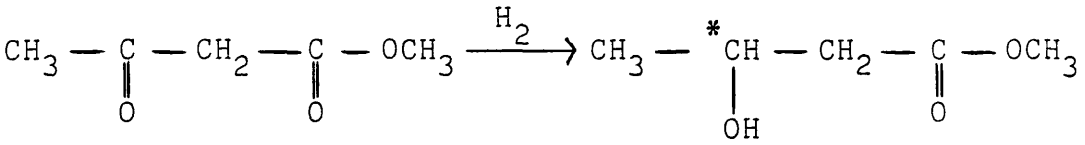


With the advent of asymmetric hydrogenation of compounds containing a C=O bond, however, Raney nickel was to find an entirely new role - that of an enantioselective catalyst.

1.7 Modified Raney Nickel Catalysts.

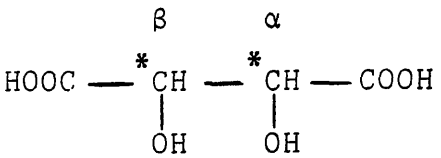
1.7.1 First Reports on Modified Raney Nickel

The first detailed reports on the use of asymmetrically modified Raney nickel catalysts in the liquid phase hydrogenation of carbonyl compounds was made by Izumi[54] in 1963. He observed that the reaction which afforded the highest optical yields was that involving the β-keto ester methyl acetoacetate:-



Methyl acetoacetate, MAA (R)- & (S)-Methyl 3-hydroxy butyrate, MHB.

Catalysts were modified with an optically active α-amino or α-hydroxy acid in aqueous solution, the pH of which had previously been adjusted to a particular value. The catalyst thus modified was then thoroughly washed before it was used in the hydrogenation reaction. Izumi reported that α-hydroxy acids as well as α-amino acids were effective asymmetric modifiers;[55] tartaric acid, for example,

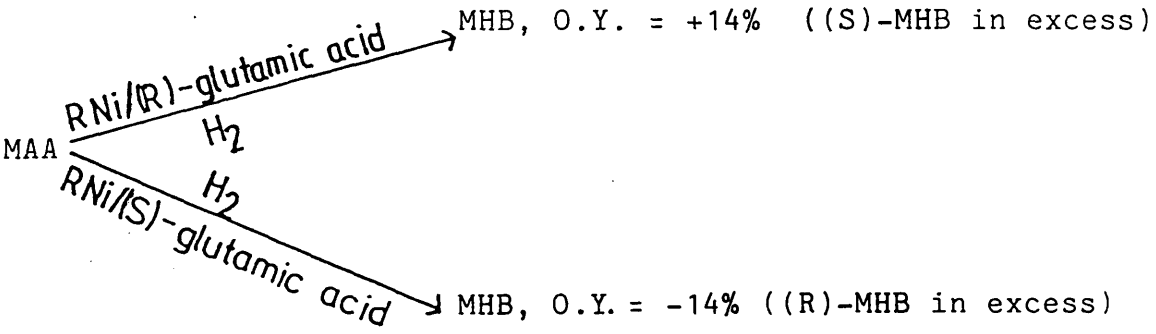


provided an optically active stereoisomer was used, and not the optically inactive meso form (see Section 1.2.2).

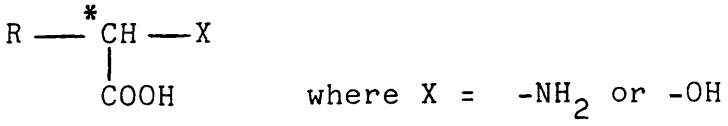
Certain general conclusions could be drawn from Izumi's reports regarding the structures and effects of suitable catalyst modifiers.

(i) The optical yield was found to be proportional to the enantiomeric composition of the modifier. Thus, maximum optical yield was attained with either pure (R)- or pure (S)-modifier†, while a value of zero was obtained with racemic modifier.

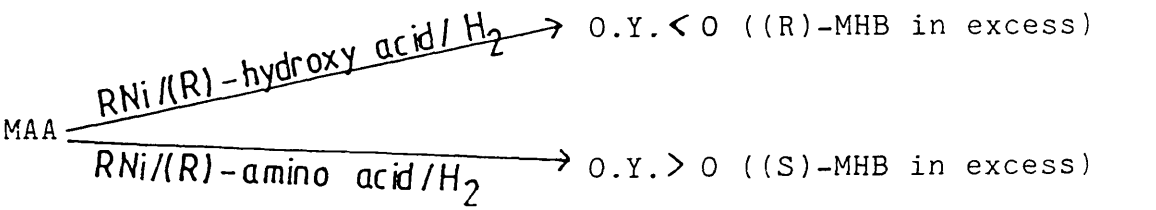
(ii) Changing the configuration of the α-carbon in the modifier resulted in a reversal in enantioselectivity; for example, the effect on the optical yield (denoted by O.Y.) using glutamic acid was as follows:-



(iii) The general structure of the most effective modifiers was that of an α-amino or α-hydroxy acid, that is

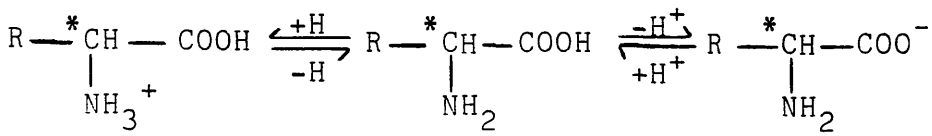


However, amino and hydroxy acids of the same configuration resulted in opposite enantioselectivities:-



(†:- denotes configuration around α-carbon atom).

(iv) An optimum optical yield was attained for a particular pH of modifying solution. For amino acids, this pH corresponded to the isoelectric point of the acid, that is, where, in the equilibria



the concentrations of the conjugate acid and base are equal. For hydroxy acids, the optimum pH was normally around 5.0 - 6.0.

(v) Modifiers could possess additional chiral centres to that at the α-carbon atom.

As a result of the interesting results which were obtained from these initial studies, a more extensive series of investigations was then undertaken by various groups in an effort to establish conditions of catalyst modification and reaction which afforded the highest optical yields in liquid phase hydrogenation reactions.

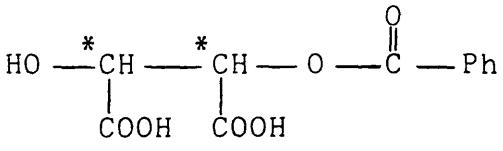
1.7.2 The Effect of the Modification Procedure

There are six possible variables in the catalyst modification procedure - the modifier itself, pH, temperature and concentration of the modifying solution, the catalyst immersion time and, lastly, the presence and identity of any co-modifiers.

The effect of altering the nature and number of

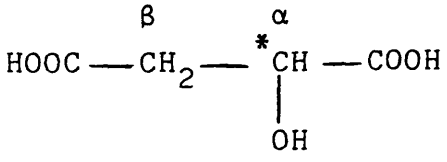
functional groups and α- and β- carbon substituents within the modifier has been investigated. Although the precise role of each was not fully clarified, several general points could be made. All investigations were based on α- amino or α - hydroxy acids.

(i) Replacing the -COOH group with, for example, the corresponding alcohol group, $-CH_2OH$, resulted in a decreased optical yield.[56] A similar effect was observed when N-substituted α-amino acids[55] or α-hydroxy acids, for example

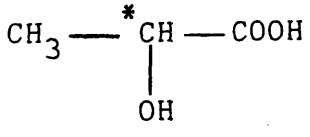


were tested as modifiers. Thus, the presence of one -COOH group and an unsubstituted $-NH_2$ or -OH was required.

(ii) For both α-amino and α-hydroxy acids, the presence of a second -COOH group increased the optical yield[57]; for example, malic acid proved to be a superior modifier to lactic acid:-



malic acid

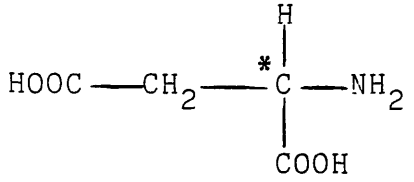


lactic acid

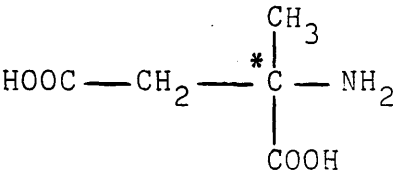
The effect of replacing a β- or γ-COOH with $-SO_3H$ was to decrease the optical yield[58] and so it was concluded that the electronegativity and bulk of this $-SO_3H$ (both greater

than for -COOH) did not affect the catalyst in a simple way.

(iii) Replacing the α-H atom with some bulkier substituent resulted in decreased optical yields for amino acids[59] - for example, aspartic acid is a better modifier than 2-methyl aspartic acid:-



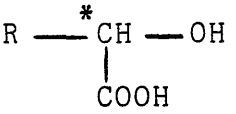
aspartic acid



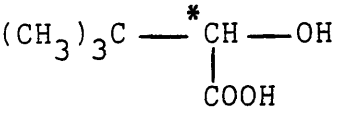
2-methyl aspartic acid

A similar effect was found for α- hydroxy acids.

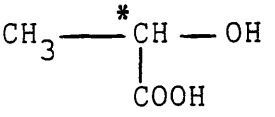
For α- hydroxy acids, the surprising result was found that increasing the bulk of the α- substituent R in



resulted in an increased optical yield[60]; for example,



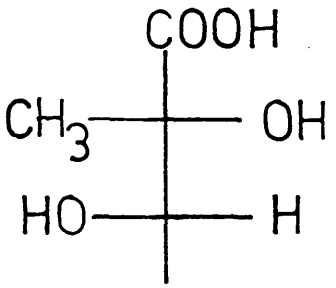
was a better modifier than



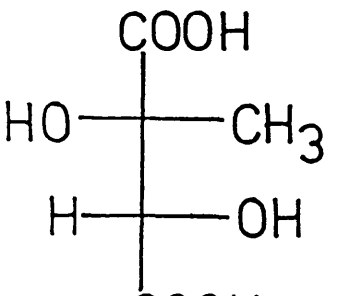
The opposite trend was found for amino acids.

(iv) If a modifier had two chiral centres, the configuration at the β- carbon was found to be important. For example,

in the case of 2-methyl tartaric acid, which has two, non-identical chiral centres, the threo isomers,

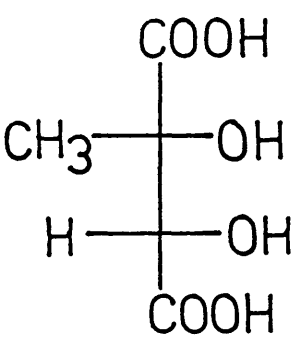


(2R,3R) and

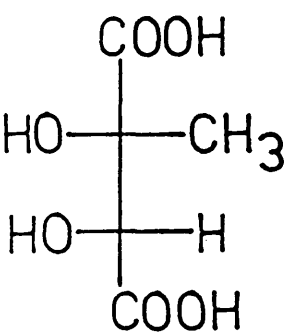


(2S,3S)

produced an even better optical yield than that obtained with tartaric acid. In contrast, the erythro isomers,

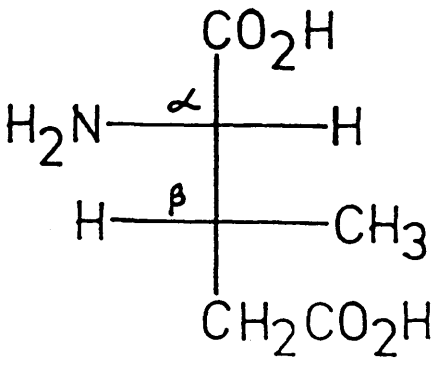


(2R,3S) and



(2S,3R)

were almost totally ineffective as asymmetric modifiers. This must have been due to the difference in configuration between the threo and erythro isomers, that is, the configuration at the β-carbon.[61] This same superiority of the threo over the erythro isomers as modifiers was also found for amino acids[62] and, in addition, the effect of the β-substituent was investigated using threo and erythro 3-methyl-glutamic acids, which, respectively, have the structures



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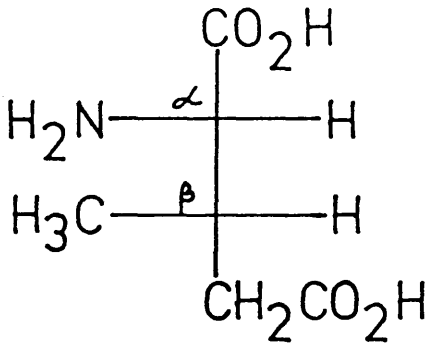
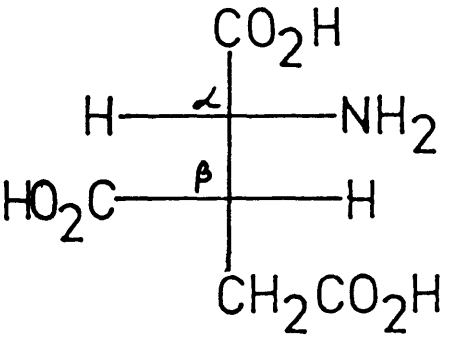
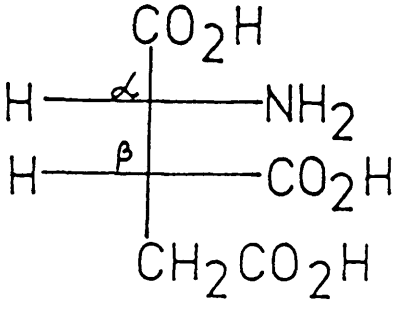


and also threo and erythro 2-amino carballylic acid, the respective structures of which are



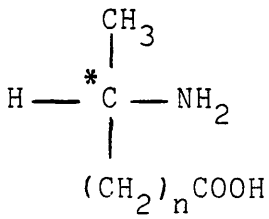
and



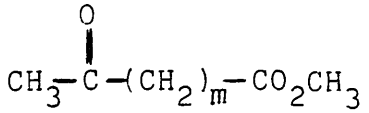
However, no simple effects were observed and it was concluded that the effect of the β-substituent depended on bulk as well

as electronic factors. Furthermore, it had become apparent that β-substituent effects were different for amino versus hydroxy acid modifiers.

(v) When a variety of α-, β- and γ-keto esters were hydrogenated over catalysts modified with α-, β- and γ-amino acids, a striking selectivity was observed.[63] Optimum enantioselectivity was obtained using an α-modifier, that is,



with n = 0, in conjunction with a β-keto ester substrate, that is



with m = 1. However, moderate optical yields were obtained using a β-acid (that is, n = 1) with a γ-keto ester (that is, m = 2) while γ-amino acids (n = 2) afforded optical yields of zero, regardless of which substrate was used. Thus, the positions of the amino acid $-NH_2$ and $-COOH$ groups relative to those of the $-\overset{O}{\overset{\|}{C}}-$ and $-\overset{O}{\overset{\|}{C}}-OCH_3$ in the substrate was a crucial factor in determining the enantioselectivity of hydrogenation.

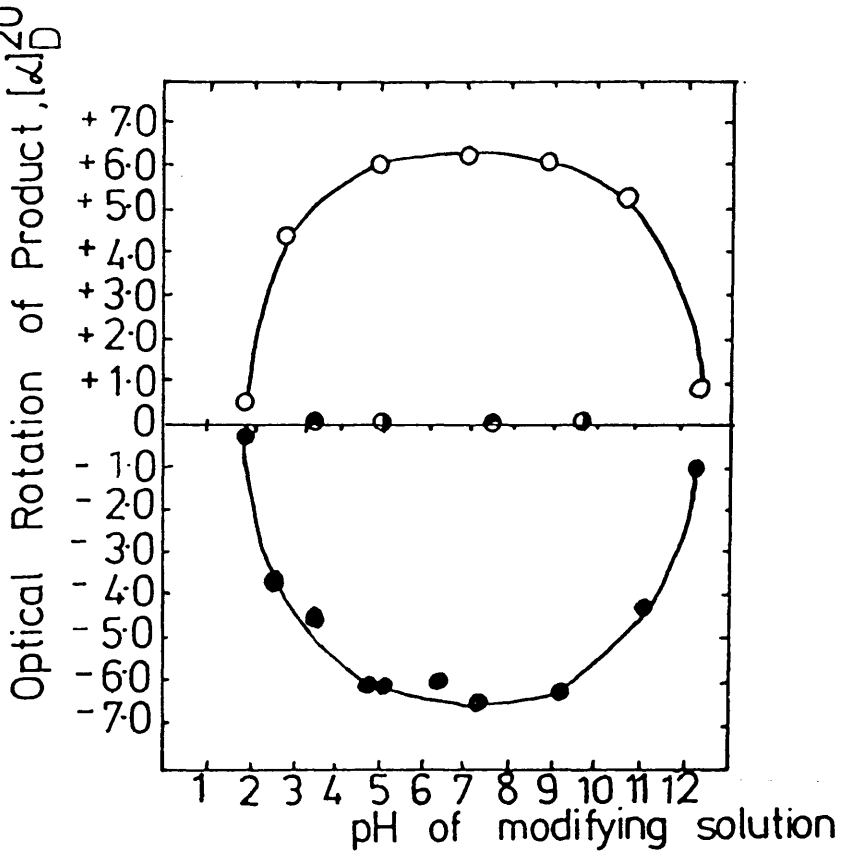
(vi) Since at least a -COOH group and either an α-OH or $-NH_2$ group were prerequisite for a modifier to be effective, the inference was that it was perhaps chelated to the Ni

surface. Thus, metal chelates, such as [Ni((L)-valine)$_2$] (where valine = $(CH_3)_2CH^*CH(COOH)NH_2$) were tested as catalyst modifiers. Not only were non-zero optical yields obtained, but greater enantioselectivity was achieved using these metal chelates as opposed to the amino acids themselves.[64] However, there was a complete lack of hydrogenation in the absence of Ni metal, and so both bulk metal as well as modifier molecules chelated to metal atoms were required for enantioselective hydrogenation; the metal complex in isolation did not function as a hydrogenation catalyst.[65]

There was therefore, considerable evidence consistent with the theory that the modifier was adsorbed on to the Ni surface in the form of a chelate, leaving the β-carbon chain free to exert a stereoselective influence on the substrate as it approached the catalyst surface.

The results obtained from varying the pH of modifying solutions containing (R,R)-, (S,S)- meso and racemic tartaric acids are shown in Figure 1.7.2.1.[66] Thus, it was evident that optically active acid modifiers resulted in a catalyst with asymmetric activity, while the use of optically inactive acid, that is, meso or racemic acid, did not. In relation to the varying optical yield with pH, the effect of pH on the amount of tartaric acid adsorbed has also been investigated using both alkaline elution[66] and electrochemical techniques;[67] both sets of results indicated a decrease in fractional coverage as the modifying

Figure 1.7.2.1 Effect of pH on Optical Yield for MAA $\xrightarrow[\text{Raney Ni}]{H_2}$ MHB

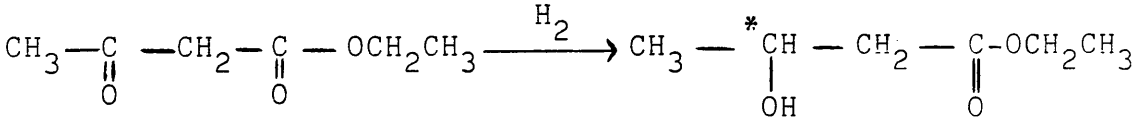


Catalyst Modifier :

- ● (R,R)-Tartaric acid
- o (S,S)-Tartaric acid
- ◑ meso-Tartaric acid
- ⊖ racemic Tartaric acid

pH increased. It was therefore apparent that, under strongly alkaline conditions, the acid must lose its ability to become adsorbed on nickel, presumably because of its conversion to the alkali salt and so this poorly modified catalyst showed very little asymmetric activity.

Similar trends of optical yield with pH were observed for other modified nickel catalysts, such as activated nickel powders and kieselguhr- and alumina-supported nickel.[68] In contrast, however, a totally different effect was observed by Klabunovskii[69] using modified nickel and copper-nickel catalysts, prepared by reduction of the corresponding oxides, in the hydrogenation of ethyl aceto-acetate:-



Ethyl acetoacetate Ethyl 3-hydroxy butyrate

It was found that two maxima for the optical yield occurred, at pH values of about 2 and 13 respectively.

In view of the results shown in Figure 1.7.2.1, however, Izumi's group continued their investigations of tartaric acid - modified Raney nickel catalysts using modifying solutions of pH 5.0.

While the asymmetric activity of modified catalysts generally increased with elevation of the modifying temperature from 0 to 100°C,[66] the hydrogenation activity simultaneously

decreased by a considerable amount.[57] This was attributed to an intensified interaction between modifier and metal at higher temperatures, causing the reagent to spread itself over the metal surface; consequently, a catalyst with many asymmetric centres was produced, in spite of its decreased hydrogenation activity.

When Raney nickel was modified with an aqueous solution of tartaric acid, the optical yield increased sharply as the acid concentration increased until the latter reached a value of 0.4%. No further increase in optical yield was observed on using modifier concentrations ranging from 0.4 to 10.0%.[66] Consequently, modifier concentrations of 1% were usually used in the investigations which followed.

A similar trend was observed on varying the immersion time of Raney nickel in the modifying solution; no further increase in optical yield was observed on prolonging the immersion time from 30 to 120 minutes. Thus, in past experiments, an intermediate immersion time of 60 minutes was normally used.[66]

About twenty years after the first reports on modified Raney nickel catalysts had appeared, alternative nickel catalysts modified with tartaric acid were proving to possess excellent enantio-differentiating abilities; for example, Orito reported an optical yield of almost 90% in the hydrogenation of MAA to MHB using a nickel-palladium catalyst[70] supported on kieselguhr. This was a considerably better result than the optical yield of 39% which was the

highest obtainable with modified Raney nickel.[71] The relatively poor asymmetric activity of Raney nickel was thought to be caused by the presence of residual aluminium, or hydrated alumina.

However, the fact remained that Raney nickel was a superior catalyst in terms of hydrogenating activity. Thus, it was desirable to develop a procedure for the preparation of an aluminium-free Raney nickel catalyst and so achieve high enantioselectivity without the simultaneous sacrifice of hydrogenation activity.

Removal of aluminium as water-soluble aluminium chelates was possible on the addition of some hydroxy-acid and it was in fact found that this process and that of modification was combined if tartaric acid was used as the hydroxy acid in conjunction with a modifying temperature of 100°C.[68]

During the course of studies on modified Raney nickel catalysts it was noticed that the optical yield of reactions was influenced by the presence of minor, supplementary compounds in the supplied water for the modification process; the effect of chloride and sulphate ions was of particular significance.[71] This phenomenon led to the idea of modifying Raney nickel with a solution containing some supplementary compound as well as tartaric acid. As a result of using an inorganic salt as the supplementary reagent, or "co-modifier", catalysts with superior enantiodifferentiating abilities were produced. The catalyst modification procedure combining aluminium removal with

the inclusion of a co-modifier was therefore:-

$$\text{Raney Ni} \xrightarrow[\text{high temperature}]{\text{aq. solution of tartaric acid/co-modifier}} \text{Modified Raney Ni}$$

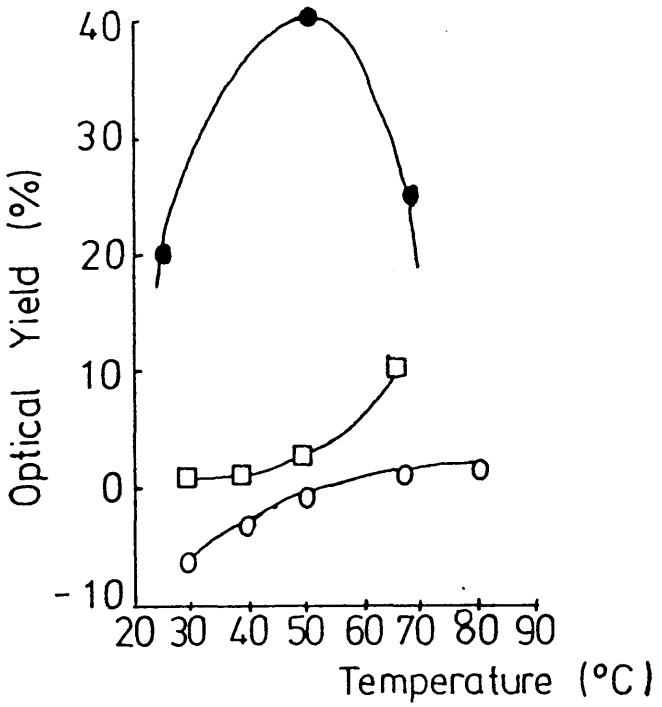
Of the inorganic salts tested, sodium bromide gave the best result with respect to enantioselectivity and activity. The optimum pH was found to be about 3.2 in conjunction with a modifying temperature of 100°C and concentration of 1 and 10% in tartaric acid and sodium bromide respectively. Under these conditions, an optical yield of 83% was obtained; this was increased to almost 90% on repeating the modification process twice.[68] Therefore, the aim to improve the asymmetric activity of modified Raney nickel while maintaining its excellent activity for hydrogenation had been successfully achieved.

1.7.3 The Effect of Reaction Conditions.

There are five possible variables in the conditions under which a reaction can be carried out - temperature, pressure of hydrogen, solvent, catalyst:substrate ratio and the identity and amount of any additives in the reaction mixture.

Some interesting temperature effects have been reported for modified Raney nickel catalysts; the results for atmospheric pressure hydrogenation of MAA using a variety of modifiers are shown in Figure 1.7.3.1.[72] Thus, in the case of amino acid modifiers, a change in temperature

Figure 1.7.3.1 Effect of Temperature on Optical Yield for MAA $\xrightarrow[H_2]{}$ MHB



● (S,S) - Tartaric acid
o L - Alanine
□ L - Glutamic acid

often caused a reversal in the direction of enantioselectivity while, for tartaric acid, an optimum optical yield occurred at a reaction temperature of about 55°C.

Careful studies of the effect of hydrogen pressure on the optical yield of MHB, obtained from the hydrogenation of MAA with a silica-supported modified nickel catalyst, were carried out by Nitta,[73] who reported a decrease in optical yield when the pressure was raised to 10kgcm^{-2}. On raising the pressure from 10 to about 90kgcm^{-2}, however, the optical yield increased from about 20 to 40%. Pressure dependences were also reported using modified Raney nickel in the hydrogenation of EAA by Klabinovskii[74,75]; unfortunately, neither group could offer an explanation for the results which had been obtained.

Optical yields obtained on using solvents varying in dielectric constant were compared by Klabinovskii, who found that, to a good approximation, the log of the optical yield varied inversely with the magnitude of the dielectric constant. Consequently, alcohol solvents were more suitable for use in reactions than, for example, ethyl acetate or n-heptane. Attempts to find a rational explanation for the results observed were made, but, unfortunately, these attempts were unsuccessful.[76]

Throughout many investigations made by Izumi and co-workers, hydrogenation reactions were in fact performed in the absence of any solvent, or, rather, MAA itself was the reaction solvent. However, this was only possible when

hydrogen pressures greater than atmospheric were used since, at atmospheric pressure, the substrate tended to corrode the catalyst.[77]

The effect of varying the ratio of catalyst to substrate in the hydrogenation of EAA using a tartaric acid - modified Raney nickel catalyst has been investigated and two, apparently different sets of results were obtained.[75] Again no explanation was offered for the observed results, which are shown in Figure 1.7.3.2.

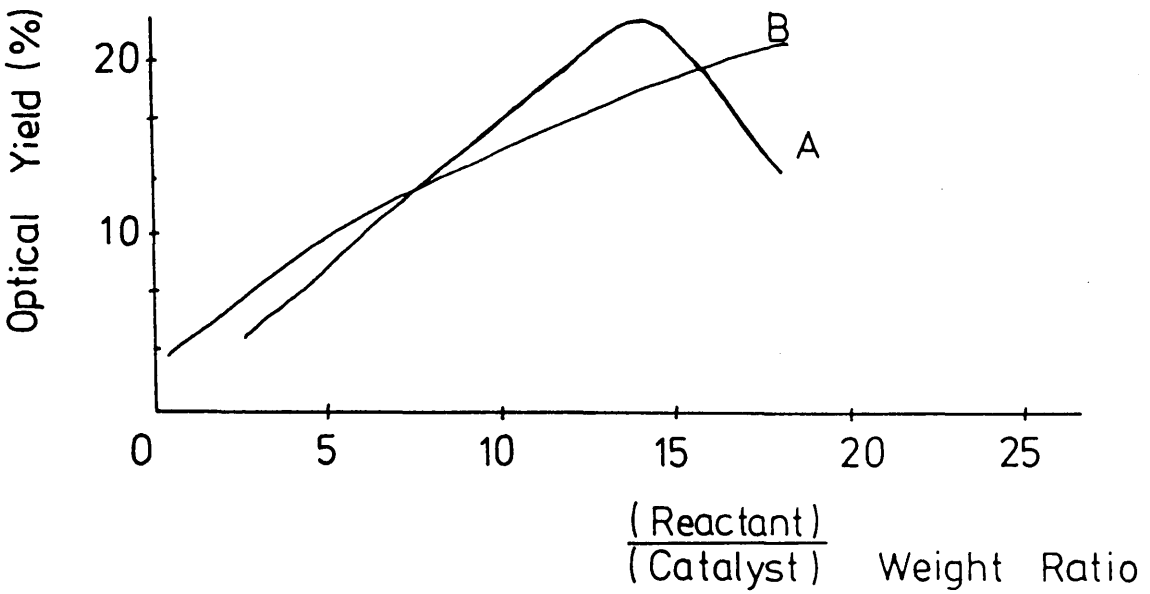
It has been reported that the addition of certain compounds to reaction mixtures can have rather spectacular effects. Water, for example, was found to have a detrimental effect on optical yields of MHB obtained on using amino acid-modified Raney nickel catalysts;[78] however, it has also been observed that the overall rate of hydrogenation was increased when trace amounts of water were added to non-aqueous solvent systems, both in the case of hydroxy as well as amino acid modifiers.[62] The suggestion at the time was that some kind of interaction may have been present between the water and adsorbed modifier molecules.

A quite different situation occurred when the carboxylic acid acetic acid was added in small amounts to reaction mixtures containing MAA. In fact, a very small enhancement in optical yield was obtained[79] which, however, was much greater in the case of monoketone hydrogenation[80], an observation which is discussed in Section 1.7.4.

Figure 1.7.3.2 Effect of Catalyst:Substrate Ratio for

$$EAA \xrightarrow[H_2]{} EHB$$

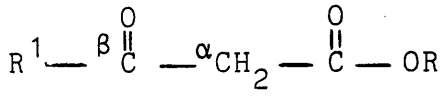
A:-0·5g catalyst, initial weight of EAA varied.
B:-5·0g EAA, initial weight of catalyst varied.



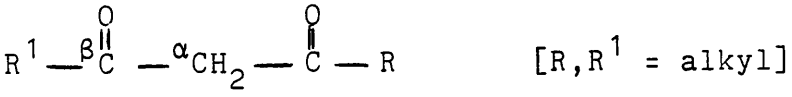
Finally, an increased optical yield of MHB resulted from the presence of trace amounts of compounds containing C=O or C=C double bonds, although no actual hydrogenation of these compounds themselves was observed.[81]

1.7.4 Substrates in Asymmetric Hydrogenation using Modified Raney Nickel Catalysts.

In the early stages of investigations into modified Raney Ni catalysts, the only suitable substrates for asymmetric hydrogenation were found to be β-ketoesters,



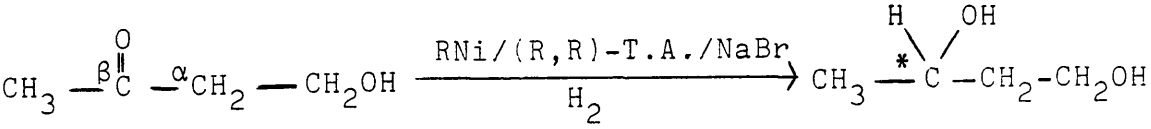
and β-diketones,[82]



[R,R^1 = alkyl]

However, as progress was made in the development of the catalysts the range of enantioselective hydrogenation reactions which could be carried out simultaneously increased.

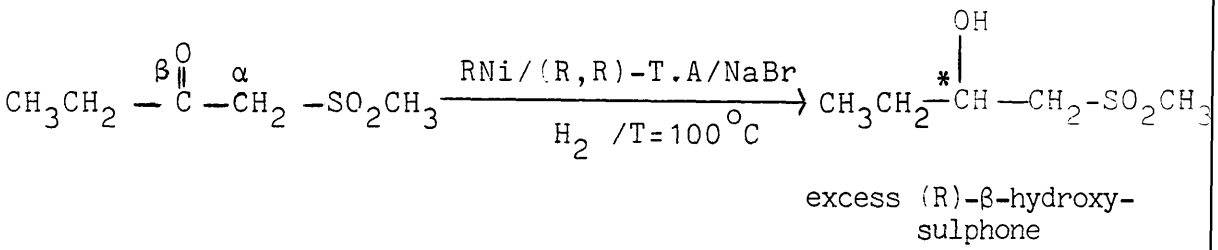
For example, Raney Ni modified with both (R,R)-tartaric acid and sodium bromide proved to be an excellent catalyst in the hydrogenation of β-keto alcohols,[83] for example



excess (R)-butane-1,3-diol

On carrying out two, successive modifications of the Raney Ni, instead of only one, the optical yield in this reaction was increased from 60 to 70%.

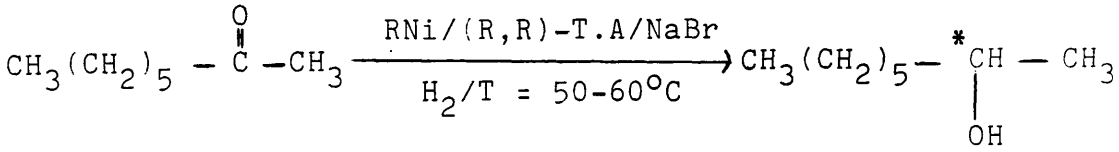
Using the same modifier and co-modifier for Raney Ni, asymmetric hydrogenation of β-keto sulphones[84] was achieved, for example:-



excess (R)-β-hydroxy-sulphone

An enantiomeric excess of 70% was obtained. Thus, the enantioselectivity was in the same direction, regardless of whether the substrate was a β-ketoester, β-keto alcohol, β-diketone or β-keto sulphone; that is (R,R)-tartaric acid modifier favoured the production of the (R)-enantiomer of the chiral product. This suggested that the mechanism of enantioselectivity was the same in each case.

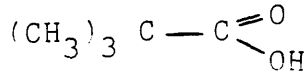
A more recent advance has been success in the asymmetric hydrogenation of monoketones[85] for example



octan-2-one

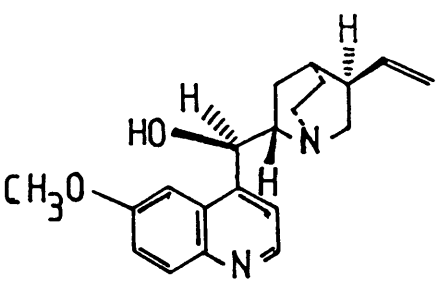
octan-2-ol (excess (S)-obtained)

The optical yield was increased from 0 to as much as 80% on addition of a small amount of pivalic acid,

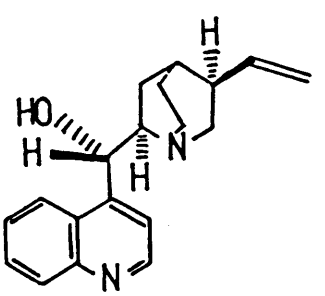


to the reaction mixture. Further investigations led to the discovery that the durability of the asymmetric catalyst was greatly improved if sodium pivalate was added to the reaction mixture.[86]

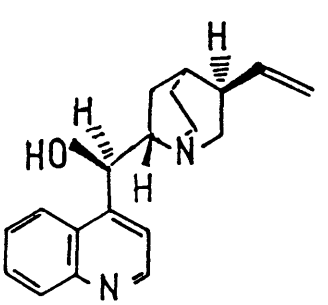
The fact that the asymmetric hydrogenation of α-keto esters was not achieved using modified Raney nickel catalysts was pointed out in Section 1.7.2.1(iv). However, Orito[87] has reported optical yields of over 80% when hydrogenation was carried out in the presence of a platinum catalyst modified with an optically active alkaloid, such as quinine,



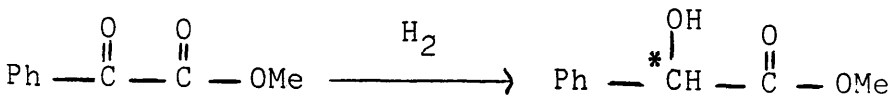
cinchonine,



or its stereoisomer, cinchonidine,



For example, an optical yield of 81.5% was obtained in the reaction



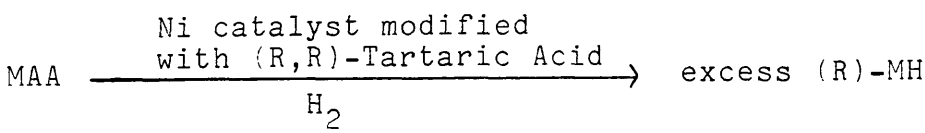
[(-)-enantiomer obtained in excess]

using a Pt/C catalyst modified with cinchonidine.

1.8 Supported Nickel Catalysts

The enantioselective hydrogenation of MAA has also been achieved using modified nickel catalysts supported on, for example, kieselguhr[88,89] silica and alumina.[65] It has been shown, however, that the support does exert an influence on the asymmetric activity of catalysts; Hoek and Sachtler[65] found that, on replacing silica with alumina, the optical yield of MHB decreased, while Izumi et al.[68] reported that the enantio-differentiating ability of kieselguhr - supported catalysts was affected by using kieselguhr from different sources.

Despite these effects on the magnitude of the optical yield, the support did not alter the direction of enantioselectivity. Thus, irrespective of whether a nickel catalyst is supported or unsupported and, in the former case, of the exact identity of the support, the reaction which occurs is



-that is, the direction of enantioselectivity is entirely dependent on the configuration of the optically active modifier.

There are, however, many possible variables in the preparation of a supported nickel catalyst and it has been shown that almost all of these preparation variables affect the selectivity of the resulting catalysts. For the case of silica-supported nickel, these observations were attributed to a change in crystallite size distribution of nickel with a change in preparative conditions.[90] This was consistent with results obtained earlier for unsupported nickel catalysts,[91] such as nickel boride, nickel phosphide and Raney nickel. The general conclusion was that the presence of small crystallites was undesirable because of the fact that they possessed only a low enantioselectivity but, also, a high overall hydrogenation activity. In contrast, larger crystallites had a higher enantioselectivity.[92] The explanation which was given was that larger crystallites had a higher probability of possessing large ensembles of regularly arranged surface nickel atoms, on which the modifier could adsorb strongly and regularly. In relation to this, Hayashi and Nagayama have recently reported that particles of nickel metal with a uniform size of 30nm exhibited very high enantioselectivity.[93]

The conditions of reduction as well as of preparation have been reported to affect the crystallite size distribution, and hence the asymmetric activity, of supported nickel

catalysts.[94] Orito et al. have reported that modified nickel-platinum metal-kieselguhr catalysts are higher in both activity and enantioselectivity than a nickel-kieselguhr catalyst[88] and this favourable effect of the platinum has been attributed to a stimulating action of the metal during the reduction process. Another point of interest which arose was the effect of the counterion of added platinum metal, which was normally in the form of platinic chloride. Nitta[95] et al. studied the effect of added chlorine, in the form of palladium chloride, on the behaviour of nickel-silica catalysts and found that, while palladium scarcely affected the asymmetric activity of catalysts, chlorine had the effect of increasing the enantioselectivity by means of increasing the mean crystallite size of nickel metal. Thus, it had been discovered that the addition of a halide to the catalyst during the reduction process resulted in an enhancement in enantioselectivity similar to that observed on including an alkali halide in the modifying solution.

In spite of this promoting effect of both platinum and chlorine on the performance of nickel catalysts, the fact remained that tartaric acid-modified platinum catalysts were found to exhibit very low enantioselectivities in the hydrogenation of β-diketones and β-ketoesters.[96]

1.9 The Mechanism of Enantioselective Hydrogenation

1.9.1 Kinetics

In the event of a proposal being made for the

mechanism of any chemical process, it must be the case that this mechanism is consistent with the observed kinetics. For the hydrogenation of MAA in the presence of a nickel catalyst modified with optically active tartaric acid, the kinetic parameters are as shown in Table 1.9.1.

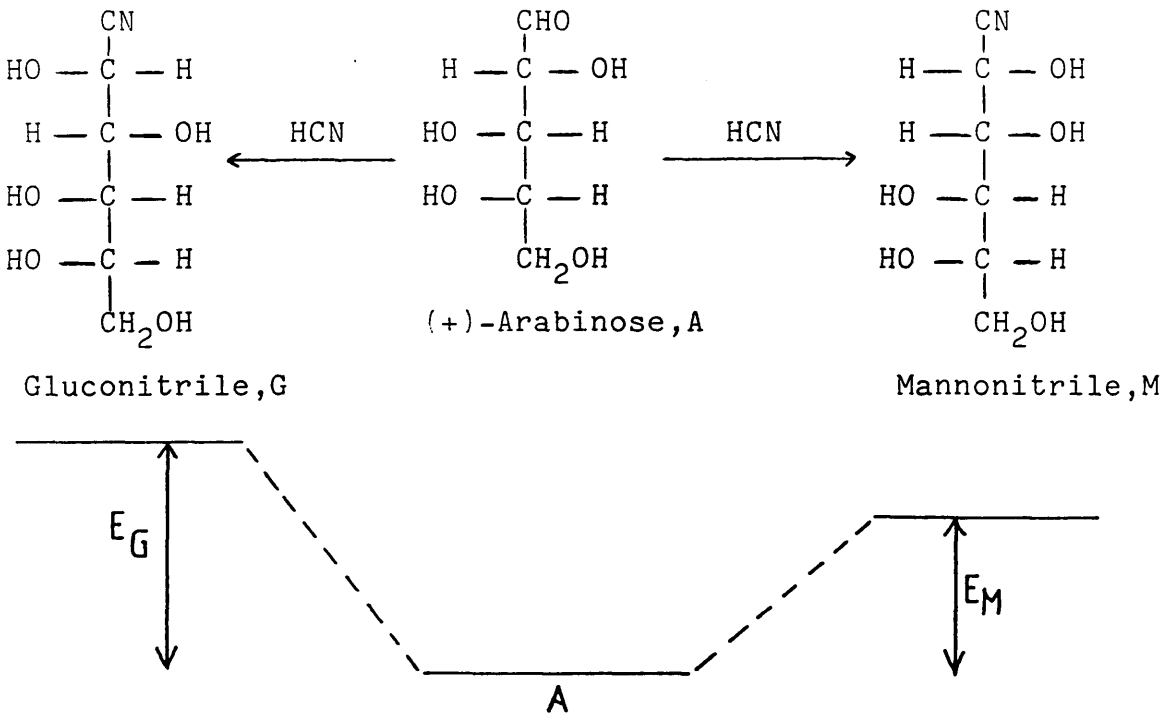
Table 1.9.1.

Phase of Reaction	Gaseous [97]		Liquid [72] (no solvent)	
Hydrogen Pressure	100-300 torr		atmospheric	
Catalyst	Ni powder (prepared from Nickel formate)		Raney Ni	
	unmodified	modified	unmodified	modified
Reaction order in MAA	1.0± 0.1	1.1± 0.1	-	0.2-0.3
H_2	0.0± 0.1	0.0± 0.1	-	0.0±0.1
Activation Energy ($kJ\ mol^{-1}$)	44.3± 2.5	43.9± 2.1	-	43.9±2.1

Thus, the value of the activation energy was unchanged on modifying the catalyst with tartaric acid. In addition, it has also been found that the activation energy was independent of the precise identity of an α-amino or α-hydroxy acid modifier[72], despite the resulting variations in both the rate of reaction and the optical yield obtained. The inescapable conclusion was that the nature of hydrogenation was essentially unchanged by the process of catalyst modification.

In asymmetric synthesis it is generally believed that the crucial feature is a difference in activation energy caused by a difference between the stereoisomeric transition states. An example is the synthesis of the diastereomers gluconitrile and mannonitrile from (+) - arabinose, which, together with the corresponding energy profile, is shown in Figure 1.9.1.

Figure 1.9.1.



Of the two diastereomeric transition states which can be formed, that for mannonitrile is lower in energy than that for gluconitrile and so, of the activation energies, E_M is less than E_G. Consequently, the two products are formed at different rates and it is the mannonitrile stereoisomer which is predominantly formed. Perhaps rather surprisingly, however, this theory of different activation energies for

different stereoisomeric transition states can be discounted in the case of enantioselective hydrogenation with modified nickel catalysts, as, on the contrary, the activation energy was found by experiment to be almost totally invariant. It was assumed, therefore, that the process by which the configuration of the chiral product was determined must occur prior to the hydrogenation step itself.[98] The problem had thus become one of identifying the nature of this enantioselective process, which was assumed to take the form of a stereochemical interaction between the substrate and the asymmetrically modified catalyst.

1.9.2 Mechanistic Studies.

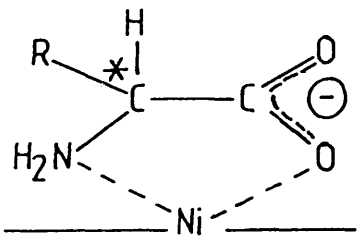
In the early 1970's a new approach to investigations on asymmetrically modified nickel catalysts was beginning to emerge. Until then, infra-red spectroscopic studies on the surface adsorption complexes of monofunctional molecules only had been published and, consequently, Groenewegen and Sachtler[99] decided to carry out similar studies on bifunctional molecules, such as amino acids, with the intention of providing answers to two questions:-

(i) Will bifunctional molecules form chelate-like complexes - that is, two bonds with one surface metal atom, or is di-adsorption on two, adjacent surface atoms preferred?

(ii) Do metal atoms remain at the surface, that is, in their original sites, during the process of chemisorption, or does corrosive chemisorption occur?

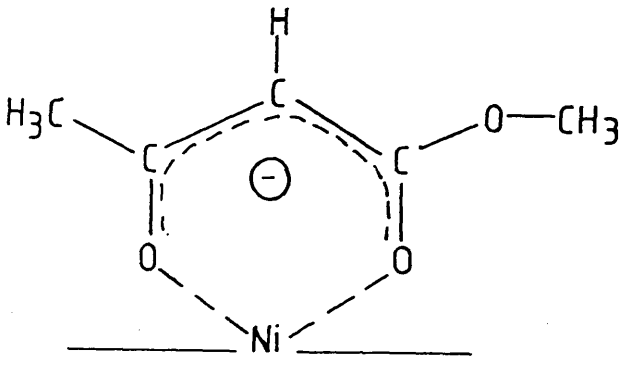
The term "corrosive chemisorption" describes the situation when adsorbent metal atoms, bonded to adsorbate molecules, move out of their original lattice sites and, simultaneously, a re-ordering of bulk metal atoms occurs. Although this rearrangement is an activated process, it can be thermodynamically more stable above a certain, minimum surface coverage.[100]

The studies on bifunctional molecules were initially centred around amino acids, one of the two types of catalyst modifiers used for the purpose of asymmetric hydrogenation reactions. The results suggested that amino acids were dissociatively adsorbed in the form of a chelate structure in its anionic form:-

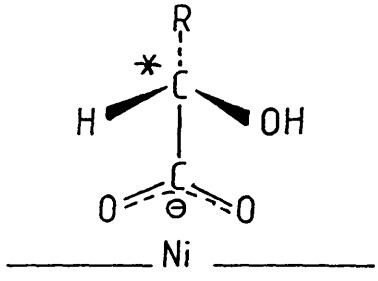


Although it was not possible to decide whether or not corrosive chemisorption had occurred using the infra-red data, tracer experiments with deuterium, D_2, had shown that complete loss of contact with the metal surface was extremely unlikely.

The structures of other types of adsorption complexes were duly given in a later report.[102] A chelate structure derived from the enol of MAA, the substrate most frequently used in asymmetric hydrogenation, was proposed:-



For α-hydroxy acids, however, the suggestion was that a carboxylate, as opposed to a chelate, was formed:-



Throughout Groenewegen and Sachtler's work using infra-red spectroscopy, the catalyst on which the adsorbed complexes were formed was silica-supported nickel.

For each of these three adsorbed complex structures, the plane of the chelate (or carboxylate) skeleton was assumed to be roughly perpendicular to the nickel surface; this was because both the infra-red spectroscopic data and the maximum degree of coverage were inconsistent with an arrangement where the chelate ring lay flat on the surface. Thus, it was also assumed that the nickel atom on which adsorption

occurred remained in the metal lattice. The mechanism which was subsequently proposed for hydrogenation in the presence of either an amino or hydroxy acid modifier is shown in Figures 1.9.2.1(a) and (b) respectively. This model is based on the various steric factors arising from the substrate being adsorbed on a nickel atom adjacent to that bonded to the modifier, and an explanation is thus given for the opposite enantioselectivities exhibited by amino and hydroxy acid modifiers of the same configuration.

However, some doubts have since arisen regarding the validity of this model.

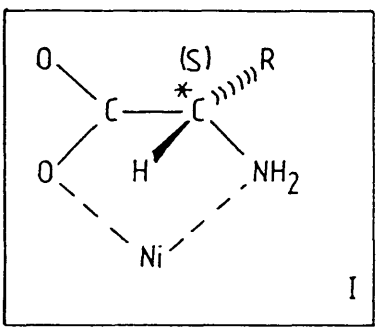
(i) First of all, since the substrate, MAA, was considered to be adsorbed in its enol form, comparatively low optical yields would be expected if a related compound, incapable of enol formation, were hydrogenated under the same conditions; an example of such a compound is 2,2'-dimethyl methyl acetoacetate, which has the structure

$$CH_3 - \overset{O}{\overset{\|}{C}} - C(CH_3)_2 - \overset{O}{\overset{\|}{C}} - OCH_3$$

Contrary to what was expected, MAA and 2,2'-dimethyl MAA were found to be hydrogenated with very similar enantioselectivities! It was therefore apparent that all thoughts concerning the substrate being hydrogenated from its enol form could be discarded. Consequently, Sachtler[65] later proposed that the active form of the substrate must be quite different from that of a stable enol, found to be present on the surface of the catalyst by infra-red studies.

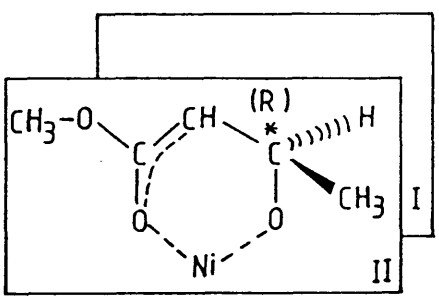
Figure 1.9.2.1 The Mechanism of Enantioselective Hydrogenation

(a) (S)- amino acid modifier

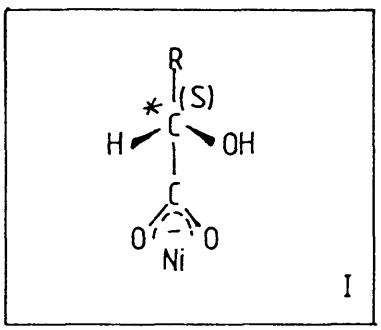


Chelate complex formed

+ $MAA_{(ads)}$

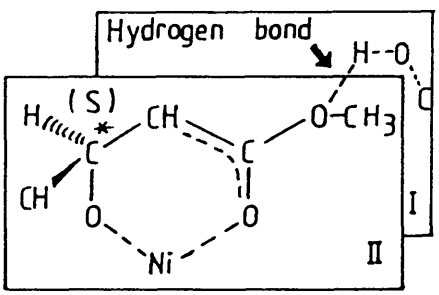


(b) (S) - hydroxy acid modifier



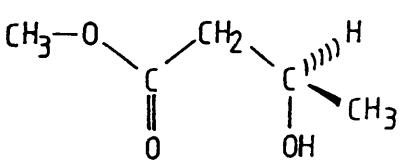
Carboxylate complex formed

+ $MAA_{(ads)}$



Planes I and II parallel ; both perpendicular to Ni surface. Relative positions of substrate / modifier determined by steric factors.

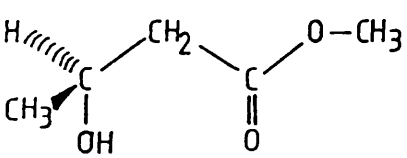
+ H_2●



(R)- MHB

i.e. (S)- amino acid ⟶ (R)- MHB

+ H_2●

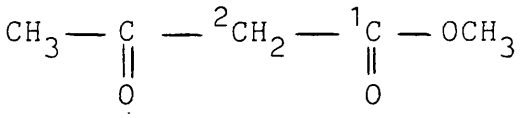


(S)- MHB

i.e. (S)- hydroxy acid ⟶ (S)- MHB

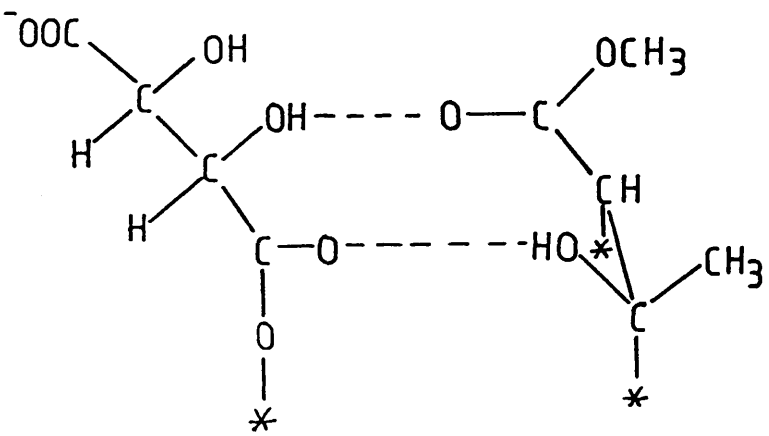
(●:- Severe steric hindrance would arise if $-CH_3$ of MAA pressed down towards plane I during addition of H_2.)

In contrast to this conclusion for liquid phase hydrogenation reactions, the suggestion of hydrogenation being carried out on the enolate of MAA was once again made, this time by Yasumori's group, with reference to reactions in the gaseous phase. This suggestion was a direct result of their observation that, during the deuteration of MAA over tartaric acid-modified Raney nickel, the hydrogen atoms on C-2 of MAA,



had been replaced with deuterium.[97] The model subsequently proposed for the interaction between MAA and tartaric acid on the catalyst surface was as shown in Figure 1.9.2.2.

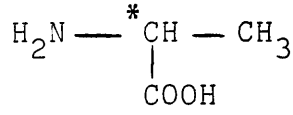
Figure 1.9.2.2.



Thus, one of each of the -COOH and -OH groups in the tartrate species,adsorbed via one -COOH group, was involved in the formation of hydrogen bonds with the enolate of MAA. Regardless of the validity of Yasumori's suggestions, however,

the fact remained that their application did not extend to hydrogenation reactions in the liquid phase.

(ii) A second factor was concerned once more with the question of whether or not modifier chemisorption was of a corrosive type; Groenewegen and Sachtler had admitted that their infra-red data was not conclusive in this respect. The idea of corrosive chemisorption was supported by Izumi's finding that similar optical yields were obtained on using nickel catalysts modified either with amino acids, for example, alanine,

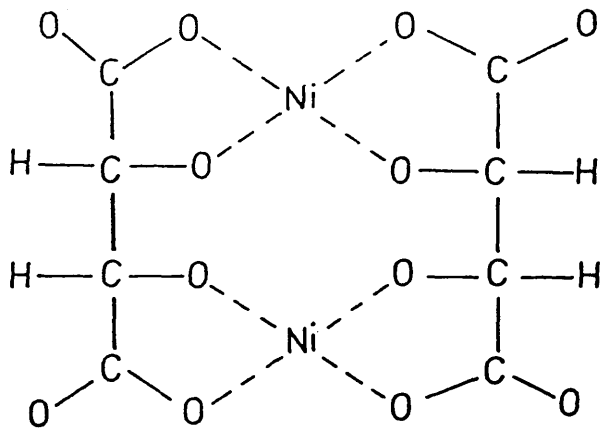


or the corresponding nickel-amino acid complexes, such as $[Ni(alanine)_2].4H_2O$.[103] Furthermore, Hoek and Sachtler[65] had become undecided as to the nature of chemisorbed tartaric acid - that is, whether, as had previously been postulated, it was adsorbed as a carboxylate, or, alternatively, as a chelate with the participation of the α-OH group; in either case, corrosive chemisorption remained a distinct possibility.

In an effort to understand more about the precise nature of the nickel-modifier adsorbed complex, Hoek and Sachtler[65] carried out an extensive series of investigations using both tartaric acid and various metal-tartrate modifiers. They concluded that there was, essentially, a Na-Ni-tartrate complex positioned on the surface of the catalyst when the optimum enantioselectivity was obtained, a proposal consistent

with Izumi's findings that the best results coincided with the use of sodium hydroxide, as opposed to other metal hydroxides, for the purpose of adjusting the modifying pH.[104] Owing to the lack of available x-ray diffraction data, it was not possible to assign a definite structure to this binuclear complex, but it was thought that an analogous structure might be that proposed by Tapscott[105] for transition metal tartrate complexes, shown in Figure 1.9.2.3.

Figure 1.9.2.3



Hoek and Sachtler then came to several conclusions regarding the overall mechanism for enantioselective hydrogenation. First of all, two types of active sites were proposed to exist on the catalyst surface; non-enantioselective sites and enantioselective sites. The former were composed of nickel atoms not disrupted from their original lattice positions and, as the name suggested, produced racemic MHB. In contrast, the enantioselective sites were composed of nickel within Na-Ni-tartrate complexes

and the direction of enantioselectivity depended on whether an (S,S)- or (R,R)-tartrate species was present.

In addition, a mechanism for the actual hydrogenation was proposed and this is summarised in Figure 1.9.2.4.

Thus, chemisorbed hydrogen atoms were not considered to be added to the unsaturated molecule directly, but, rather, the addition occurred via some chemisorbed complex, an idea first introduced by Thomson and Webb.[106] Also, an explanation for the necessity for both metallic as well as complexed nickel was given; while the latter provided the chiral "template" for enantioselective hydrogenation, the former, besides providing the active sites for non-enantioselective hydrogenation, had three functions:-

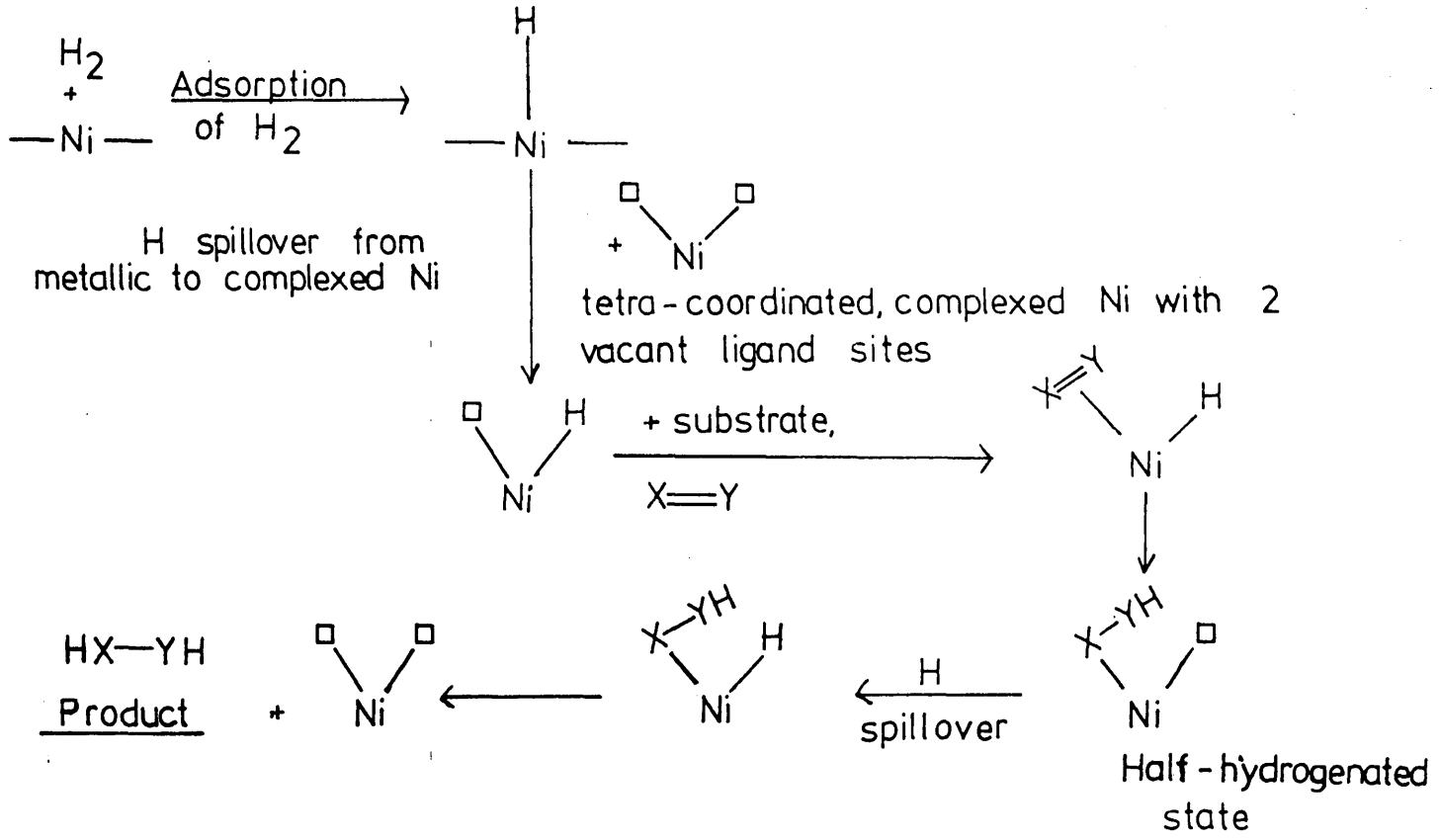
(a) it served as a surface complex carrier

(b) it enabled the initial adsorption of hydrogen, $H_2 \longrightarrow 2H_{(ads)}$

(c) it acted as a chemical reagent for the in situ formation of a Na-Ni-tartrate complex when modified with a solution of tartaric acid, the pH of which had been adjusted with sodium hydroxide.

This dual-site mechanism for hydrogenation is by no means restricted to enantioselective reactions; for example, Poels and co-workers[107] have shown that, using a palladium catalyst, the activity for converting synthesis gas, a mixture of hydrogen with carbon monoxide, was greatly increased by leaving some of the palladium ions unreduced.

Figure 1.9.2.4 The Mechanism of Hydrogenation (on enantioselective sites)



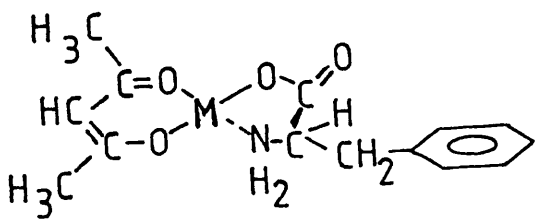
They also proved the presence of palladium ions by extraction with acetylacetone and subsequently proposed that hydrogen, dissociating on the palladium metal particles, reacted with undissociated carbon monoxide, adsorbed on the palladium ions.

As a result of further investigations carried out by Bostelaar and Sachtler[108] however, the validity of the hypothesis that the presence of a Na-Ni-tartrate complex was essential for enantioselectivity was placed in some doubt. This was due in part to the finding that, on modifying a silica-supported nickel catalyst with a solution of tartaric acid in methanol, a significant enantioselectivity was observed. The crucial point in this discovery was that this enantioselectivity had been obtained in the absence of any alkali ions, since there had been no previous addition of a solution of sodium hydroxide to the methanolic modifying solution; this was in complete contrast to the situation normally encountered when using an aqueous solution of the modifier, since the pH of this solution was always adjusted to some particular value with the aid of aqueous sodium hydroxide. Furthermore, in a separate report, the same group found that no sodium ions were incorporated into nickel (R,R)-tartrate crystals when precipitated from sodium-containing solutions.[109] However, the idea that chemisorption of tartaric acid was corrosive in nature remained firmly in favour, and so it was concluded that the presence of an adsorbed nickel tartrate was sufficient for the induction of significant enantioselectivity. Unfortunately, there were no further suggestions as to the precise nature of

the interaction between the substrate and adsorbed modifier complex.

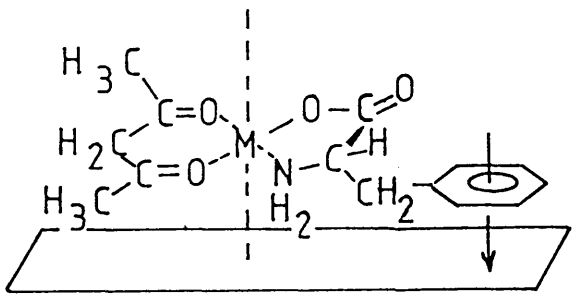
Despite the fact that Sachtler's group had succeeded in presenting an extremely detailed account of the mechanism of hydrogenation of MAA, the same amount of detail had been omitted from their description of the origin of enantioselectivity, since the structures of the adsorbed substrate and modifier complexes, and hence the mechanism of enantiodifferentiation, shown in Figure 1.9.2.1 were no longer considered to be valid. However, two models which attempt to describe the process of enantioselectivity are currently in existence.

The first alternative model, proposed by Klabunovskii *et al.*, concerned the hydrogenation of acetylacetone, AA, and ethyl acetoacetate, EAA, in the presence of various Raney catalysts. The suggestion was that a heteroligand chelate complex, ML_1L_2, where L_1 and L_2 were the substrate and modifier, was formed on the surface of the catalyst.[110] A model for this complex, where, for example, L_1 was AA and L_2 (S)-phenylalanine, was considered to be



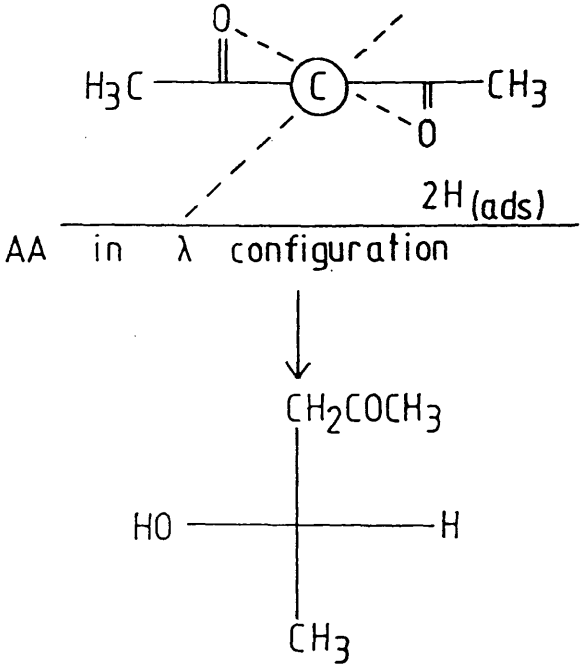
The actual structure of the complex, when situated on the catalyst surface, was presumed to be as shown in Figure 1.9.2.5.

Figure 1.9.2.5.



By means of studying the circular dichroism spectra obtained for various surface heteroligand complexes, it was concluded that an induced chirality was present in the substrate ligand, which was due to a puckering of this β-dicarbonyl molecule in either a λ or δ configuration.[111] Taking this induced puckering into account, a mechanism for enantio-selective hydrogenation was proposed. For the example of AA hydrogenated over a Cu-Ni catalyst, modified with (S)-phenylalanine, the mechanism was as shown in Figure 1.9.2.6.

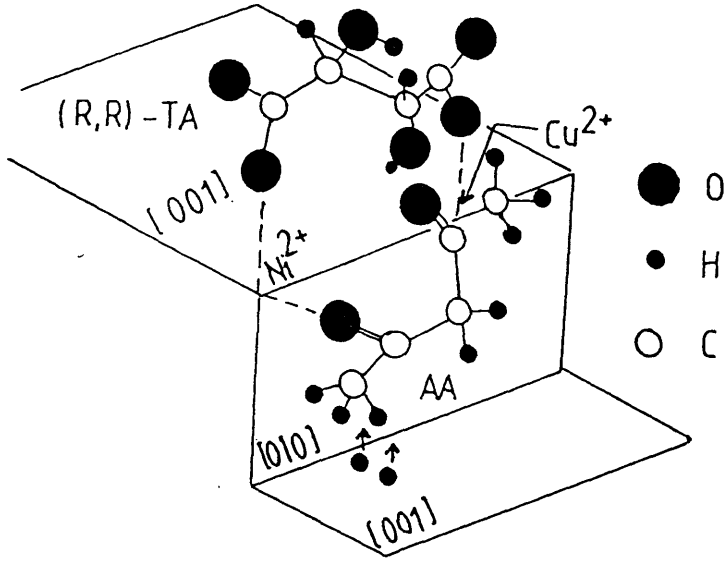
Figure 1.9.2.6



(S) - 4 - hydroxy - pentan - 2 - one in excess

Circular dichroism spectra of surface heteroligand complexes were obtained for a wide range of modifiers in an effort to compile a very detailed list of correlations between the conformational distortion of the substrate ligand and the direction of enantioselectivity. In conjunction with these studies, a model for the structure of tartaric acid adsorbed on a copper-nickel catalyst was proposed on the basis of investigations using infra-red spectroscopy. Tartaric acid was considered to form a surface chelate, while it was felt that the results obtained were best explained by supposing that enantioselective hydrogenation occurred only at stepped sites within the metal surface. The stereochemical model which was proposed is shown in Figure 1.9.2.7.

Figure 1.9.2.7



Apart from presenting the completely novel idea of catalysis at stepped sites on the metal surface, there are several important features in this model:-

(a) There is only one site possible for hydrogen bonding between the substrate and modifier.

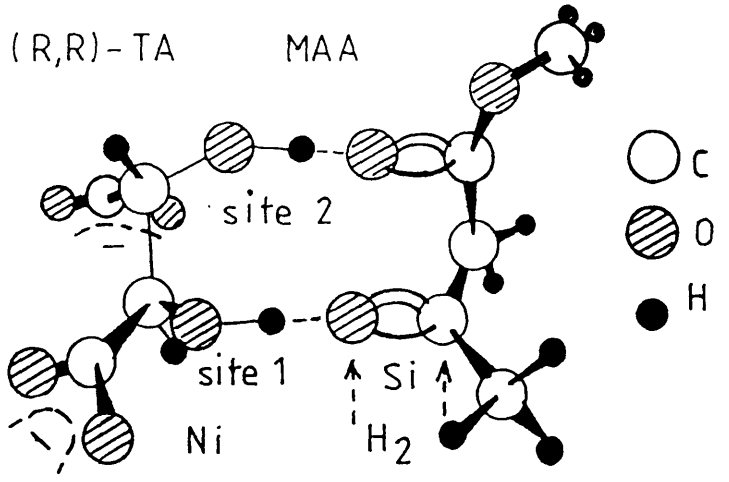
(b) The two -COOH groups in the tartaric acid species are bonded to a Ni^{2+} and Cu^{2+} ion respectively; the -OH groups are not involved in bonding to the metal surface.

(c) There is no suggestion of any corrosive chemisorption - the two metal ions involved remain in the bulk metal.

Izumi's group was responsible for the second alternative model to that proposed by Hoek and Sachtler. Its main concern was the mode of interaction between the substrate and modifier on the surface of a Raney nickel catalyst, with the emphasis once more on tartaric acid and

MAA as the modifier and substrate respectively. The mode of interaction which was suggested[112] is shown in Figure 1.9.2.8.

Figure 1.9.2.8.



Again, there are several features which are important:-

(a) Two sites of hydrogen bonding exist between the substrate and modifier.

(b) The tartaric acid modifier is attached to the metal surface by both -COOH groups.

(c) In view of the observation previously mentioned that the enantioselective hydrogenation of species incapable of enol formation has been successfully carried out, the substrate, MAA, in Figure 1.9.2.8, is adsorbed in its keto form.

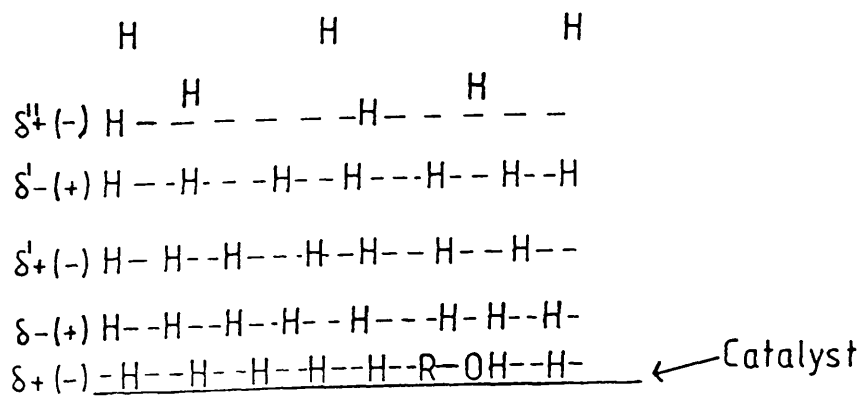
(d) Adsorption was presumed to occur on a flat nickel surface, without the simultaneous occurrence of any corrosion.

Another feature common to both of Klabunovskii's and Izumi's proposals was that adsorbed hydrogen was assumed to be added to the adsorbed substrate directly from the surface of the catalyst. However, Izumi's group have recently postulated that the nature of hydrogen addition is in fact a process of greater complexity than was at first thought[113]; their alternative hypothesis can be separated into three successive stages:-

(i) Following the formation of a chemisorbed monolayer of hydrogen on the metal surface, further layers of physically adsorbed hydrogen were added.

(ii) Transmission of the polarisation induced by the chemisorbed layer of hydrogen to hydrogen molecules in the upper part of the multi-molecular layer occurs; this phenomenon is represented in Figure 1.9.2.9, in which it is shown that polarisable substances other than hydrogen, such as alcohols, can also serve as transmitters of polarisation.

Figure 1.9.2.9



(iii) The subsequent hydrogenation reaction can occur at that particular position in the multilayer of hydrogen where favourably polarised hydrogen molecules are available. The example of hydrogenation of a C=O group is likely to take place at a site distant from the surface of the catalyst; this is because the highly polarisable C=O group will require the presence of highly polarised hydrogen.

1.9.3 The Origin of the Effect of Alkali Halides.

The phenomenon of promotion in heterogeneous catalysis was first recognised over seventy years ago, when Jobling[114] made the observation that, on the addition of a minute quantity of some foreign substance, the activity of a catalyst could be greatly increased. For instance, during the synthetic manufacture of ammonia by means of the Haber process,

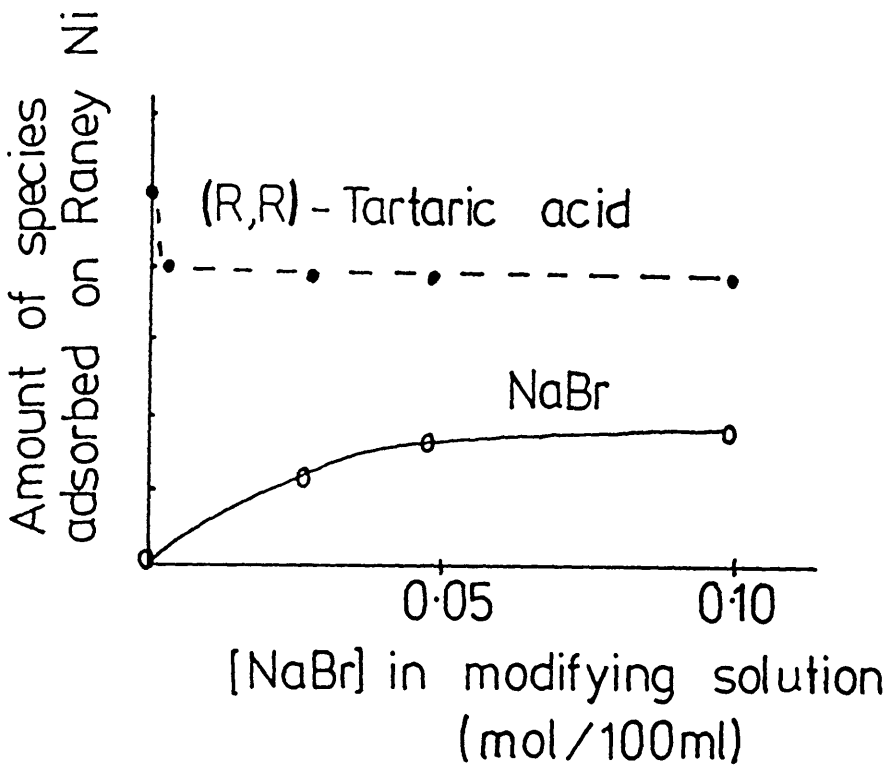
$$3H_{2\ (g)} + N_{2\ (g)} \longrightarrow 2NH_{3\ (g)}$$

the metal catalyst is vastly improved by the presence of traces either of salts of other metals or, alternatively, of the other metals themselves.[115] A second example involves Raney nickel; it has been established that the addition of small amounts of sodium hydroxide or platinic chloride enhances the activity of the catalyst for C=O and N=O hydrogenation respectively.[116] Support effects, site creation and electronic or geometric effects represent just some of the current beliefs as to the mechanism by which the various promoters operate.[115]

The fact that the inclusion of an alkali halide as a co-modifier has a tremendous influence on the behaviour of nickel catalysts has already been mentioned in Section 1.7.2. Initially, it might be thought that this merely provides one more example of the promotion effect which has just been described. However, there is a fundamental feature which differentiates this role of an alkali halide from that of a conventional promoter - the overall activity of the nickel catalysts for C=O hydrogenation has been found to remain constant or decrease, as opposed to increase. It follows that any mechanism which is suggested for this action of alkali halides must be intrinsically different from that of a typical case of promotion. However, it must also be true that a suggested mechanism must be consistent with whatever is to be believed regarding the mechanism of enantioselective hydrogenation in the absence of any co-modifier. Two, quite different theories concerning the origin of the effect of alkali halides have been proposed, by Izumi and Sachtler's groups respectively.

Since sodium bromide was found to be a more effective co-modifier than any other alkali halide tested, the vast majority of Izumi's studies in this area used a nickel catalyst modified with tartaric acid plus sodium bromide. The results obtained from investigating the effect of adsorbed sodium bromide on the amount of tartaric acid adsorbed on Raney nickel are shown in Figure 1.9.3.1.[117]

Figure 1.9.3.1



It is obvious from Figure 1.9.3.1 that, with the exception of a sudden, initial decrease, there is very little change in the amount of tartaric acid adsorbed in the presence of sodium bromide. This suggests that the catalyst surface can be thought of as consisting of two parts, where one preferentially adsorbs tartaric acid while the other adsorbs sodium bromide rather than tartaric acid. Since the enantio-differentiating ability of the catalyst is greatly increased by adding sodium bromide to the modifying solution, the function of sodium bromide must be to reduce the amount of non-enantioselective hydrogenation which occurs - that is, sodium bromide is effectively

poisoning those sites which would otherwise catalyse racemic hydrogenation. Thus, the part which preferentially adsorbs sodium bromide is where non-enantioselective hydrogenation occurs, whereas most of the other part, which adsorbs tartaric acid, provides the sites for enantioselective hydrogenation. However, sodium bromide does not completely saturate the racemic sites and so a seemingly appropriate classification of the various active parts on the catalyst surface is as shown in Table 1.9.3.1.

Table 1.9.3.1

Section of Catalyst	Description of Sites
P - I + P - II	Total number of sites active in hydrogenation
P - I	Portion of sites where enantioselective hydrogenation proceeds.
P - II	Portion of sites where non-enantioselective hydrogenation proceeds
P - IIa	Portion of P-II sites which cannot be blocked by NaBr.
P - IIb	Portion of P-II sites which can be blocked by NaBr.

The rates of enantioselective and non-enantioselective hydrogenations, denoted by E and N respectively were related by the expression

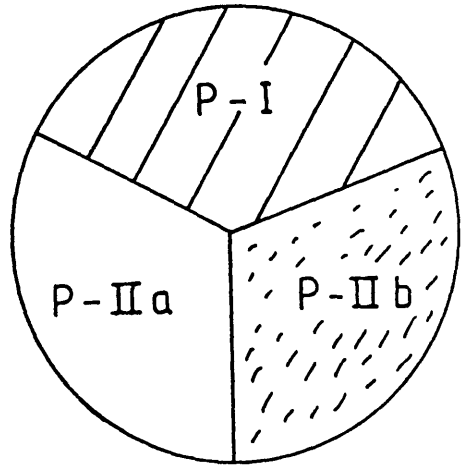
$$\frac{E}{N} = \frac{P\text{-}IIa}{P\text{-}I} + \frac{P\text{-}IIb}{P\text{-}I}(1-f) \qquad (1.9.3.1)$$

where f = degree of saturation of NaBr = $\frac{\text{amount of NaBr adsorbed}}{\text{saturation amount of NaBr}}$

It was thought that the linearity of the relation indicated that sodium bromide deactivates P-IIb by a blocking mechanism rather than reducing the rate constant of non-enantioselective hydrogenation on the P-IIb sites.

From equation 1.9.3.1, it was possible to calculate the exact proportions of parts P-I, P-IIa and P-IIb for Raney nickel modified with tartaric acid and sodium bromide, and this is represented in Figure 1.9.3.2.

Figure 1.9.3.2



It is perhaps interesting to note that there was no mention of any interaction between the modifier and co-modifier on the surface of the catalyst, since the two species were assumed to be adsorbed on totally separate sites; neither was there any attempt to describe the location of the sodium ions following the adsorption of the anionic bromide ions.

One of Sachtler's first aims was to clarify whether or not alkali halides were irreversibly adsorbed on a nickel surface, thereby blocking certain active sites. Therefore, the effect of simply adding sodium bromide to the liquid phase reaction mixture, as opposed to using the halide as a co-modifier in conjunction with tartaric acid, was investigated[108]; the results are shown in Table 1.9.3.2 for a silica-supported nickel catalyst.

Table 1.9.3.2.

Modifying Solution	2% tartaric acid (aq) pH 5.0 10% NaBr	2% tartaric acid (aq) pH 5.0	2% tartaric acid (aq) pH 5.0
Concentration of NaBr in reaction mixture ($mmol^{-1}$)	-	-	†10
enantiomeric excess (%)	29	24	55

†:- Concentration of NaBr which gave optimum enantiomeric excess.

It was obvious from these results that, on dissolving sodium bromide in the reaction mixture, a significant enhancement of the enantioselectivity was obtained. Bostelaar and Sachtler[118] continued their investigations in this area in two ways; the relative amounts of various alkali halides adsorbed on the catalyst were examined using x-ray fluorescence measurements and, in addition, the relationship between enantiomeric excess and the concentration of alkali halide in the

reaction mixture was determined in some detail. It was claimed that three results in particular were inconsistent with Izumi's simple model of preferential site-blocking:-

(i) For sodium bromide, the marked enhancement in selectivity was found to occur in spite of the fact that the activity remained virtually constant.

(ii) With lithium bromide, no selectivity enhancement took place at salt concentrations which were sufficient to decrease the activity.

(iii) For iodides and sodium bromide, a decrease in enantiomeric excess was found at high salt concentrations, which indicated a preferential blocking of selective, rather than of non-selective sites.

It was felt, therefore, that some consideration must be given to the possibility of stereochemical interactions occurring between the salt ions and the asymmetric sites.

Thus, Bostelaar and Sachtler were convinced that the corrosive interaction of tartaric acid with a nickel surface led to the formation of nickel tartrate, a process which resulted in parts of the modified catalyst being covered with layers of this tartrate species. They suggested that the enantioselective sites could then be located on the edges and corners of such nickel tartrate sheets; this was in some way consistent with a proposal made earlier by Klabunovskii, which was described in Section 1.9.2. The existence of hydrogen bonding between

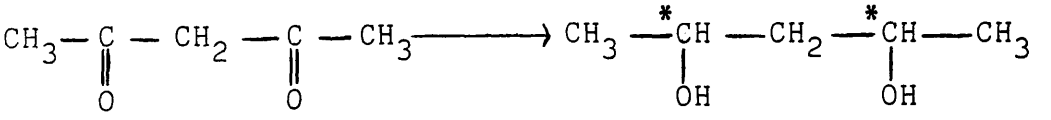
substrate and modifier was once again recognised, although not described. The point was made that, since electro-neutrality had to be maintained, the concentration of adsorbed alkali ions, from an alkali halide co-modifier, was dependent on the degree to which the halide anion was adsorbed; while the location of these alkali ions could not be positively identified, it was thought that complexation with the oxygen atoms within the adsorbed tartrate species might be occurring. Although it appeared conceivable that this was the manner in which the stereochemistry of the "nickel-tartrate - substrate" was altered, thus providing a logical reason for the considerable influence of alkali halides, the possibility that the blocking of non-selective, or even selective sites by ions may be occurring could not be completely discarded.

1.9.4 Final Comments

Despite the fact that a great variety of effort has been channelled into attempts to elucidate the mechanism of enantioselective hydrogenation, the picture remains far from clear. Indeed, the enormous complexity of the subject is perhaps reflected in Izumi's group having apparently directed their attentions from mechanistic studies to improvements in the durability of asymmetrically modified catalysts. The process which has been developed involves embedding a Raney nickel catalyst in an oxime-type, room temperature vulcanising silicone polymer matrix; the catalyst has normally been modified with both tartaric acid and sodium

bromide. A catalyst prepared in this way resulted in an enantiomeric excess of over 60%, even after thirty times of repeated use, whereas this high enantioselectivity was lost after a mere three times of repeated use under normal circumstances.[119] It has also been reported that the durability of the catalyst can be further improved to maintain an enantiomeric excess of over 70%, provided a small amount of an amine, such as pyridine, was added to the modifying solution containing the tartaric acid and sodium bromide.[120]

However, in spite of the lack of a proper mechanistic understanding, asymmetrically modified Raney nickel catalysts are at present employed during the commercial preparation of optically active alcohols from ketones, for example, the production of pentan-2,4-diol[121] from acetylacetone:-



It is perhaps ironic that the chiral alcohols produced in this way serve as starting materials for the preparation of optically active diphosphine ligands, which are later used in the form of rhodium-diphosphine complexes as homogeneous asymmetric hydrogenation catalysts.

CHAPTER 2

OBJECTIVES OF THIS STUDY

The objective of the work described in this thesis was to investigate in detail the asymmetric hydrogenation of prochiral substrates on suitably modified metal catalysts, in particular the use of Raney nickel catalysts modified with the optically active stereoisomers of tartaric acid for the hydrogenation of β-keto esters. To achieve this objective the hydrogenation of methyl acetoacetate to methyl 3-hydroxy butyrate was studied, with particular reference to:-

(a) Possible methods of quantitative analysis of enantiomeric mixtures using chromatographic, spectroscopic and polarimetric techniques.

(b) A detailed examination of conditions for (i) preparation of the Raney nickel catalysts from nickel:aluminium alloy and (ii) the successful modification of these catalysts by pretreatment with optically pure tartaric acid alone, as well as in conjunction with alkali metal halides.

(c) Investigations of the influence of solvent, water content of solvent and variations in reaction temperature and hydrogen pressure on the conversion and enantioselectivity.

CHAPTER 3

EXPERIMENTAL

3.1 List of Chemicals Used.

The following is a list of all chemicals used:-

Chemical	Source	Purity
Acetic Acid (glacial)	Koch-Light	99%
Acetic Anhydride	Hopkin & williams	98%
Benzene	BDH	99.7%
Butan-1-ol	BDH	99.5%
Caesium Bromide	Aldrich	99.9%
(R)-(+)-trans-Chrysanthemic Acid	Sigma	99.8%
Deuterochloroform	Sigma	99.8%
Diethyl Ether	Koch-Light	99%
N,N-Dimethyl Formamide	Fluka	99%
Ethanol	Koch-Light	99.5%
Ethyl Acetate	Formachem	99.5%
Hydrochloric Acid	May & Baker	99%
(L)-(+)-Lactic Acid	Aldrich	99%
Methanol	May & Baker	99.5%
(S)-(-)-α-Methoxy Trifluoro-methyl Phenyl Acetic Acid	Aldrich	99%
Methyl Acetoacetate	Aldrich	98%
(R)-(-)-Methyl 3-Hydroxy Butyrate	Aldrich	99%
(S)-(+)-Methyl 3-Hydroxy Butyrate	Aldrich	99%
Methyl Propionate	BDH	99%
Ni:Al Raney Alloy (50:50)	Aldrich	pure
Pyridine	Aldrich	99%

Chemical	Source	Purity
Sodium Borohydride	Koch-Light	99%
Sodium Bromide	Fluka	99%
Sodium Carbonate	Hopkin & Williams	99.9%
Sodium Chloride	Formachem	99.9%
Sodium Hydrogen Carbonate	Koch-Light	99.9%
Sodium Hydroxide	BDH	98%
Sodium Sulphate	Koch-Light	99%
meso-Tartaric Acid	Aldrich	98%
(R,R)-(+)-Tartaric Acid	Fluka	99.5%
(S,S)-(-)-Tartaric Acid	Fluka	99%
Thionyl Chloride	Hopkin & Williams	98%
Toluene	May & Baker	99%
Tris[3-(heptafluoropropyl-hydroxy-methylene)-(+)-camphorato]-europium III	Fluka	99%

It was necessary to purify some of these chemicals before use. The various methods of purification are listed below.

(i) Thionyl chloride was refluxed with sulphur to remove all sulphur-containing impurities and then fractionally distilled twice.

(ii) Toluene, benzene and diethyl ether were dried with sodium wire;.these solvents were then distilled from and stored over sodium wire. In order to remove all sulphur-containing impurities, toluene was shaken with and distilled from Raney nickel.

(iii) Butanol, ethanol, ethyl acetate, methanol, methyl acetoacetate and methyl propionate were distilled before use.

All other chemicals were used without further purification.

Nitrogen (oxygen-free), air and hydrogen gases were supplied by British Oxygen Company.

Column packings for gas chromatography, Chromosorb W, AW Chromosorb P DCMS, both of mesh size 60-80, UCON fluid and 1,2,3-tris(2-cyanoethoxy)propane were supplied by Phase Sep.

3.2 Catalyst Preparation.

3.2.1 Raney Nickel, RNi.

50:50 Ni:Al Raney alloy (1.90g) was added in portions of about 0.4g to 5M aqueous sodium hydroxide solution (20ml), cooled in an ice bath to almost 0°C. The suspension was then heated to 75°C in an oil bath and maintained at this temperature for 1 hour, after which time the alkaline solution was decanted and the catalyst washed with distilled water (15 x 30ml).

3.2.2 Tartaric Acid-Modified Raney Nickel, *MRNi.

(R,R)-(+)-tartaric acid (1.00g, 6.7×10^{-3}mol) was dissolved in distilled water (100ml) and the pH of the solution adjusted from 1.80 to the desired value, which was

within the range 1.8 - 12.0, with 1M aqueous sodium hydroxide solution using a pH meter. This solution was cooled to almost $0^{o}C$ in an ice bath and freshly prepared RNi added. The resulting suspension was maintained at this temperature for 1 hour, with occasional shaking. After decantation of the modifying solution the catalyst was washed with distilled water (1 x 30ml), methanol (2 x 30ml) and, finally, with the appropriate reaction solvent (1 x 25ml).

3.2.3 (I). Tartaric Acid/Sodium Bromide-Modified Raney Nickel,*MRNi/NaBr.

(i) (R,R)-(+)-tartaric acid (1.00g, 6.7×10^{-3}mol) was dissolved in distilled water (100ml) and heated to $100^{o}C$ in an oil bath. Freshly prepared RNi was added to this solution and, after 1 hour at $100^{o}C$, the tartrate solution was decanted and the catalyst washed with distilled water (1 x 30ml).

(ii) (R,R)-(+)-tartaric acid (1.00g, 6.7×10^{-3}mol) and sodium bromide (10.00g, 9.07×10^{-2}mol) were dissolved in distilled water (100ml) and the pH of the resulting solution adjusted from 1.25 to the desired value, which was within the range 1.8 - 12.0, with 1M aqueous sodium hydroxide solution, using a pH meter. After cooling to almost $0^{o}C$ in an oil bath, RNi from (i) was added and the suspension maintained at this temperature, with occasional shaking, for 1 hour. The modifying solution was then decanted and the catalyst washed with water (1 x 30ml), methanol (2 x 30ml) and, finally, with the appropriate reaction solvent (1 x 25ml).

3.2.3 (II). Tartaric Acid/Sodium Bromide-Modified Raney Nickel, *MRNi/NaBr

(R,R)-(+)-tartaric acid (1.00g, 6.7 x 10^{-3}mol) and sodium bromide (10.00g, 9.07 x 10^{-2}mol) were dissolved in distilled water (100ml) and the pH of the solution adjusted from 1.25 to the desired value, which was within the range 1.8 - 12.0, with 1M aqueous sodium hydroxide solution, using a pH meter. This was heated to 100°C in an oil bath and freshly prepared RNi added; the solution was maintained for 1 hour at 100°C, with occasional shaking. After this time the modifying solution was decanted and the catalyst washed with water (1 x 30ml), methanol (2 x 30ml) and,finally, with the appropriate reaction solvent (1 x 25ml).

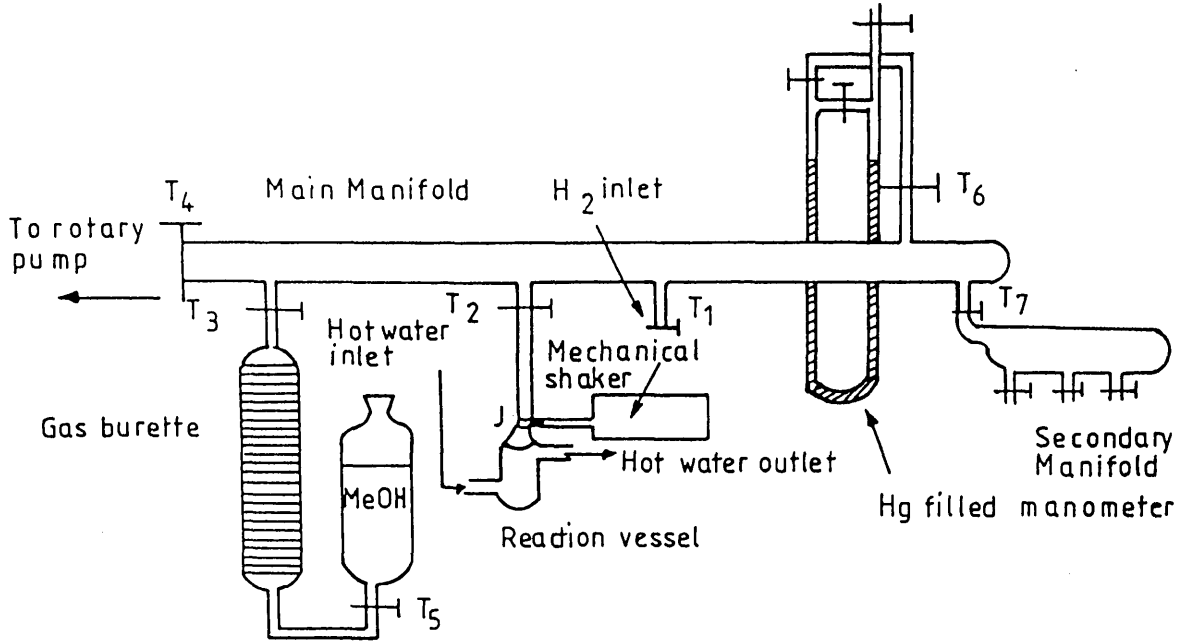
Any deviation from, for example, temperatures stated in these descriptions is clearly stated in the Results chapter.

3.3.1 Atmospheric Pressure Liquid Phase Hydrogenation System.

This apparatus, shown in Figure 3.3.1, was of the conventional high vacuum type. Using a mercury diffusion pump in conjunction with a rotary oil pump it was possible to maintain pressures of 10^{-4}torr. The efficiency of the vacuum system was further increased by the use of two liquid nitrogen traps, which were connected in series with the water-cooled diffusion pump.

Admission of gases was possible using the "Quickfit" B10 socket attached by a 4mm tap, T_1, to the main manifold

Figure 3.3.1 Atmospheric Pressure Hydrogenation Apparatus.



* Hot water inlet and outlet lead from and to a thermostatically controlled water bath.

while the two-limbed mercury manometer, also attached with a 4mm tap, T_6, allowed pressures of admitted gas to be monitored.

A methanol-filled glass reservoir was attached with flexible tubing, secured with copper wire, to a 500ml gas burette. Flow of methanol between the reservoir and burette was controlled by a 4mm tap, T_5, fitted to the reservoir. Admission of gas to the burette from the main manifold was possible through a 4mm tap, T_3.

Flexible tubing, secured with copper wire, connected the 4mm tap, T_2, to a B19 "Quickfit" cone, which was then available for attachment to the reaction vessel; this B19 cone and socket joint (J) to the reaction vessel was sealed and protected with a teflon sleeve of appropriate size. Gas was admitted to and evacuated from the vessel by means of tap T_2.

The smaller, secondary manifold was included to enable vacuum distillation to be carried out following various syntheses; this was isolated from the main manifold by a 4mm tap, T_7.

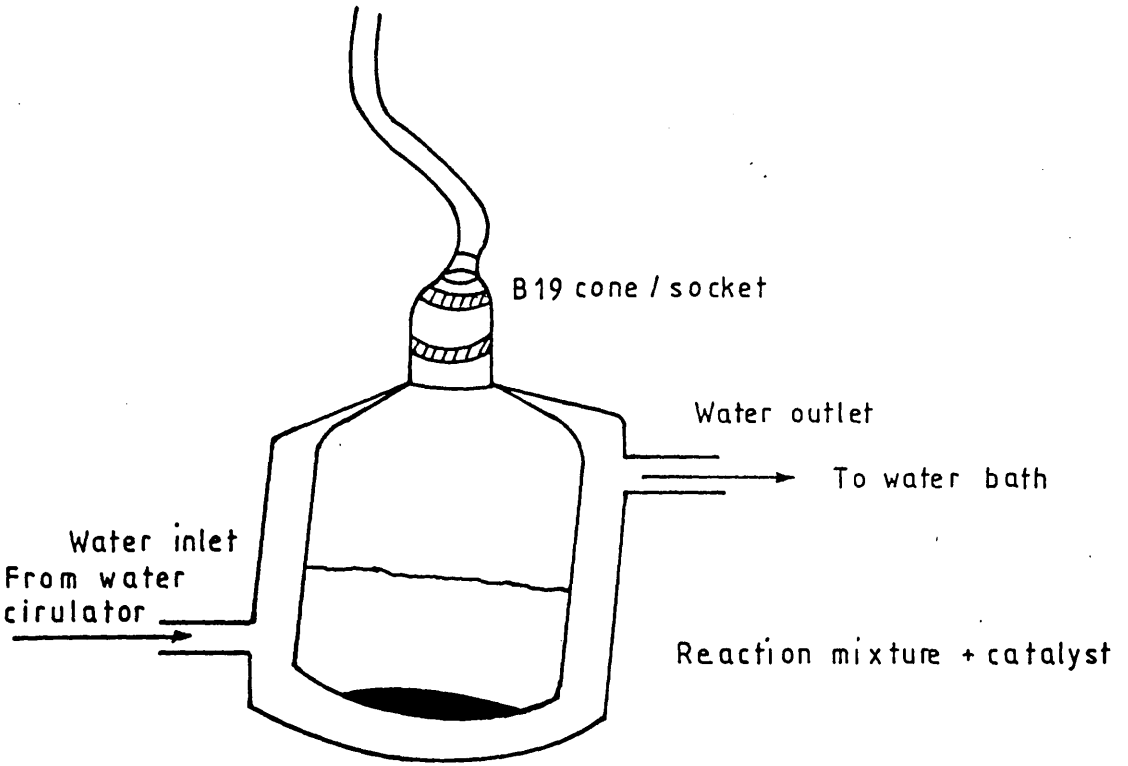
Unless otherwise stated, all cone/socket connections and taps were lubricated with Apiezon "N" grease.

3.3.2 Procedure for Atmospheric Pressure Hydrogenation.

A solution of MAA in the reaction solvent was added to the reaction vessel, together with the freshly prepared Raney nickel catalyst. The glass reaction vessel, which is shown in Figure 3.3.2, consisted of two parts; the catalyst and reaction mixture were contained in the internal part, which had a capacity of $42cm^3$. Flexible tubing, secured with copper wire, was connected from a hot water circulator to the external part of the reaction vessel, through which was flowed water, which then flowed into a thermostatically controlled water bath, again by means of flexible tubing. In this way the reacting species were surrounded by a water "jacket", and thus the reaction temperature could be accurately controlled.

The reaction vessel, containing the substrate in solution plus catalyst, was firmly clamped to a mechanical shaker and joint J was secured with a joint clip of appropriate size. When the temperature of the circulating water had reached that at which the reaction was to be carried out, the gas burette and reaction vessel were evacuated *via* taps T_3 and T_2 respectively. Hydrogen was then admitted to the system *via* tap T_1 until a pressure of 800 torr was indicated by the manometer; this hydrogen was removed immediately afterwards. This procedure was repeated three times to ensure that all air was purged from the system. After the fifth admission of hydrogen, its pressure was reduced from 800 to 760 torr in the following way:-

Figure 3.3.2 Reaction Vessel for Atmospheric Pressure Hydrogenation Reactions



(i) The glass reservoir, which was open to the atmosphere, was raised to a position such that the methanol levels in it and the gas burette were equal.
(ii) Tap T_5 was opened to allow methanol to flow from the burette into the reservoir, while, simultaneously, altering the position of the reservoir to enable the methanol levels to remain equal.
(iii) Tap T_5 was closed when the flow of methanol had resulted in the hydrogen pressure being decreased to 760 torr. Tap T_3 was then also closed.

The mechanical shaker was switched on for the duration of the reaction, thus ensuring efficient mixing of reacting species. Taps T_2 and T_6 were kept open throughout the reaction period.

At the end of the required reaction time, the contents of the reaction vessel were cooled to room temperature and the agitation stopped. Hydrogen not consumed during the reaction was removed *via* tap T_4 and, after closure of T_4, air was admitted through tap T_1 until the system attained atmospheric pressure. The reaction vessel was then removed and the reaction mixture filtered through glass fibre filter paper to free it from the pyrophoric catalyst, which was immediately rendered safe by the slow addition of concentrated hydrochloric acid.

Analysis of the reaction mixture was then carried out.

3.4.1 High Pressure Liquid Phase Hydrogenation Apparatus

This stainless steel apparatus is shown schematically in Figure 3.4.1.1. Pressures of 10^{-1} torr were obtainable by use of a rotary oil pump, while the system itself was capable of withstanding hydrogen pressures of 3000 psi.

Admission of hydrogen was possible through valve V_1 and evacuation through valve V_2; valve V_2 also served as a means of venting the system to the atmosphere. Hydrogen was admitted to the bomb itself, shown in detail in Figure 3.4.1.2, via taps T_1 and T_2. The bomb could be heated under thermostatic control and, simultaneously, set into a rocking motion.

3.4.2 Procedure for High Pressure Hydrogenation.

MAA, dissolved in the reaction solvent, was added to the glass liner, shown in Figure 3.4.2.1, together with the freshly prepared Raney nickel catalyst. The glass liner was then loaded into the stainless steel vessel, with the breathing-hole uppermost. The bomb head, compression rings and screw-collar were fitted and bolts 1-8 tightened in a diagonal sequence, illustrated in Figure 3.4.1.2. After fitting the pressure-gauge block, the stainless steel vessel was loaded into the bomb.

With valve V_1 closed, the system was evacuated via valve V_2 and taps T_1 and T_2. Valve V_2 was closed and

Figure 3.4.1.1 High Pressure Liquid Phase Hydrogenation Apparatus

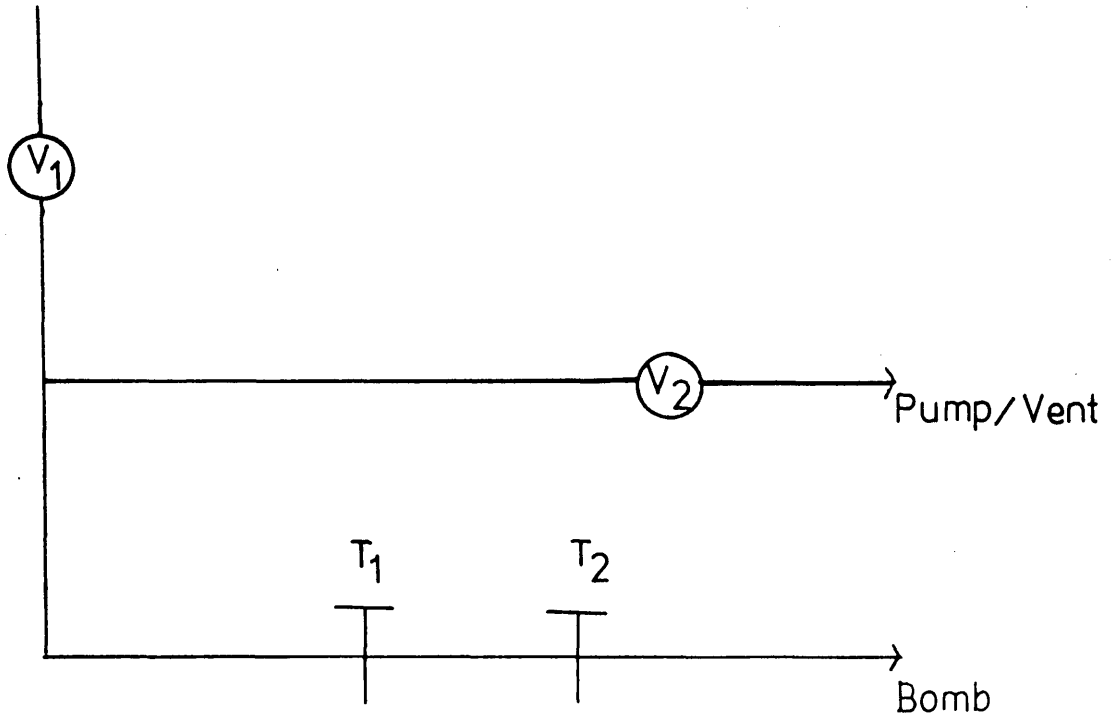


Figure 3.4.1.2 High Pressure Hydrogenation Apparatus

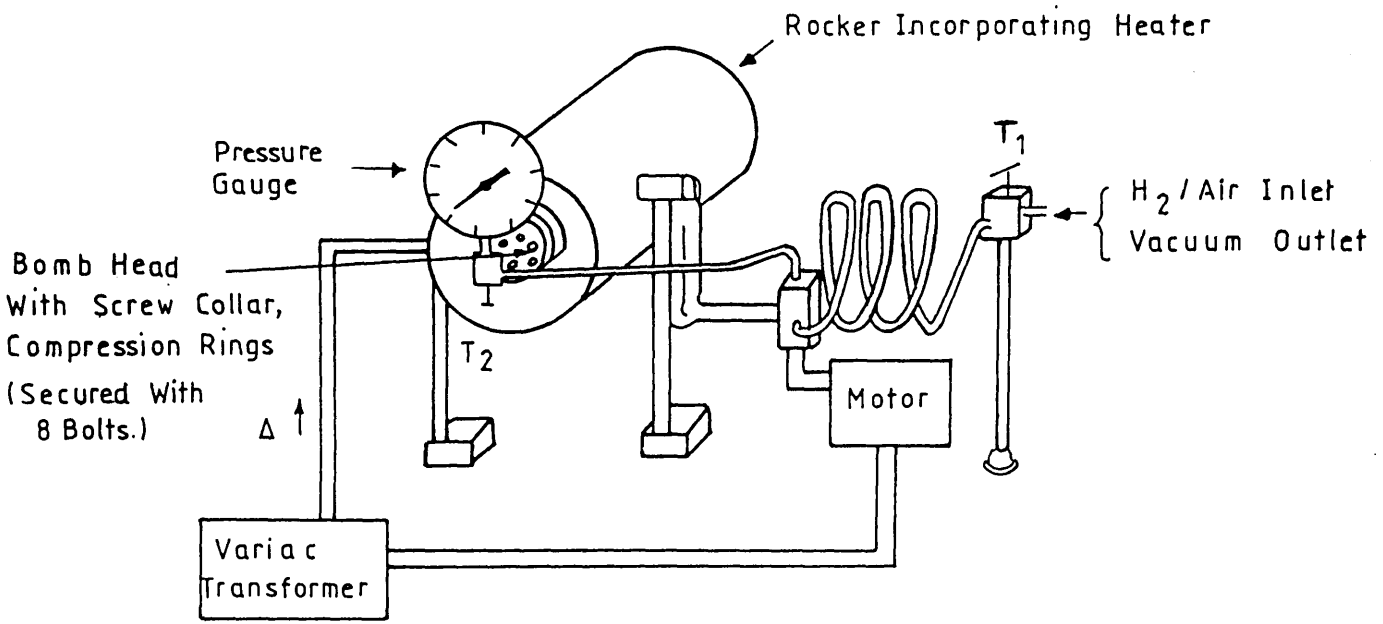
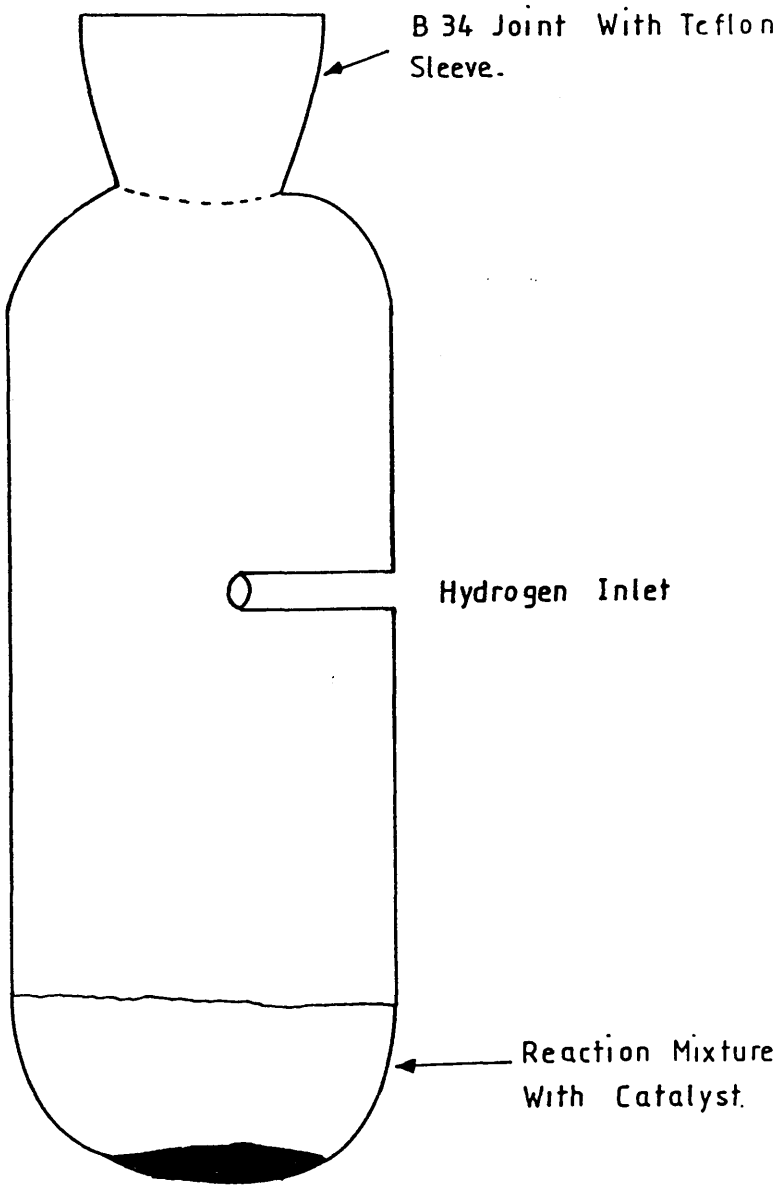


Figure 3.4.2.1 1l Glass Liner for High Pressure Autoclave

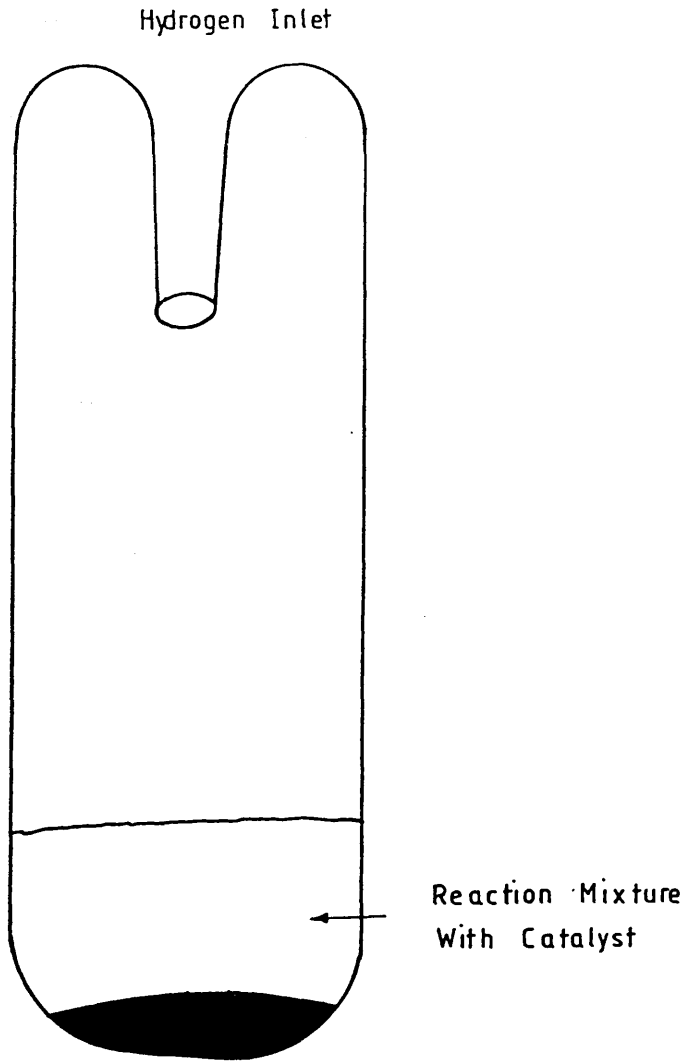


hydrogen was slowly admitted through V_1 and into the bomb, *via* taps T_1 and T_2. When the pressure-gauge registered 1000 psi, valve V_1 was closed and the system carefully vented and evacuated; air was thus purged from the system. Hydrogen was admitted once more until the pressure at which the reaction was to be carried out was attained. Taps T_1 and T_2 were closed, as well as valve V_2. Hydrogen, which was external to the bomb and tap T_2, was vented and then valve V_2 closed. Following this procedure, the bomb was set into a rocking motion and, at the same time, the bomb heater, thermostatically controlled at the desired reaction temparature, was switched on for the duration of the reaction. After hydrogenation, the system was cooled to 25°C and unused hydrogen vented. The whole system was then evacuated and, lastly, vented once more until the interior of the bomb reached atmospheric pressure.

Following the removal of the glass liner, the reaction mixture was filtered through glass fibre filter paper and then analysed; the treatment of the remaining Raney nickel catalyst was identical to that described in Section 3.3.2. Qualitative and quantitative analyses of the filtered reaction mixture were carried out by gas chromatography.

Hydrogenation reactions carried out at I.C.I., Blackley, used stainless steel apparatus very similar to that described in this section. The glass liner was also of capacity 1ℓ but differed slightly in design; a "Bergius Bomb" was used, the design of which is shown in Figure 3.4.2.2.

Figure 3.4.2.2 1l Berguis Bomb for High Pressure Autoclave



3.5 Gas Chromatography

Resolution of solvent, reactant and product contained in reaction mixtures was achieved using a 10' long, 1/4" o.d. stainless steel column, packed with a 15% W/W dispersion of UCON fluid supported on Chromosorb W. Chromatography was carried out using a Pye Unicam Gas Chromatograph fitted with a flame ionisation detector.

Figure 3.5.1 is the chromatogram of a 10µℓ sample of a typical mixture after hydrogenation of MAA at atmospheric pressure in butanol; the conditions were chosen so that resolution of MAA and MHB was complete. Nitrogen was used as the carrier gas.

Chromatographic analyses performed at I.C.I., Blackley, were carried out using a 15m long, 0.22mm i.d. stainless steel capillary column coated with OV17 of film thickness 0.25µm. The chromatogram of a typical reaction mixture in methanol is shown in Figure 3.5.2. In contrast to the packed column, use of this capillary column, under similar conditions of temperature and carrier gas flowrate, allowed resolution of MAA and MHB to be carried out much more quickly; resolution was possible in less than five minutes, as opposed to over one hour. Furthermore, the order of elution was reversed, as MHB was eluted before MAA from the capillary column.

3.6 Analysis of Enantiomeric Compositions.

Attempts to carry out purification of MHB by means

Figure 3.5.1 Gas Chromatogram of MAA/MHB Mixture in Butanol

(i) N_2 Flowrate = 90 ml/min
(ii) Detector Oven Temperature = 150° C
(iii) Column Temperature = 125° C
(isothermal)

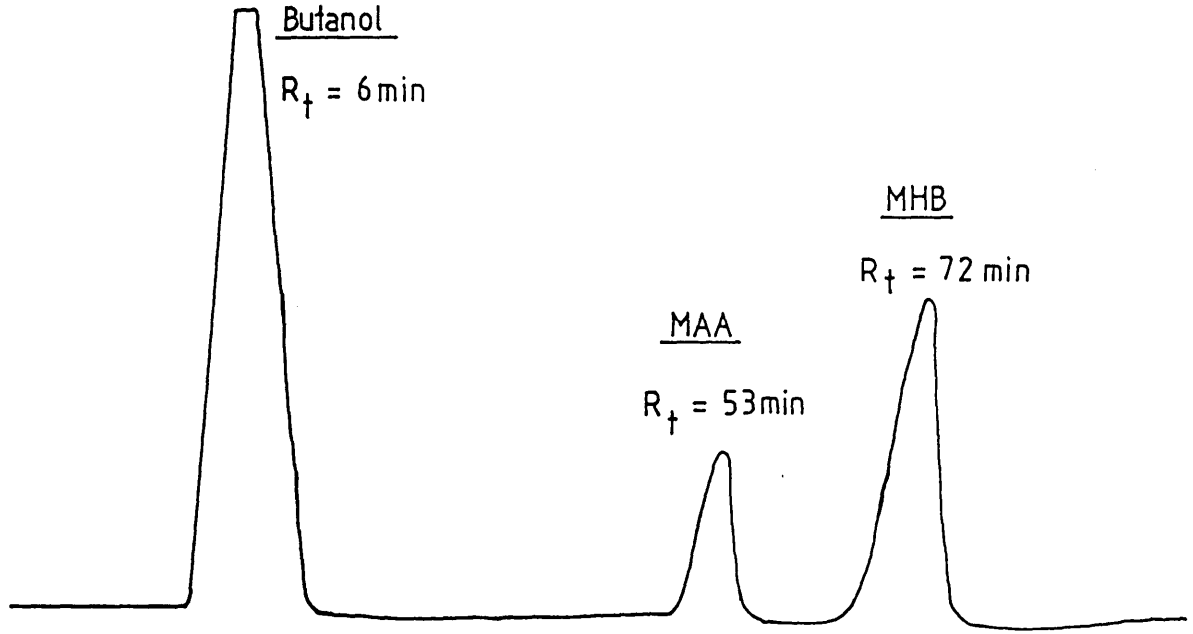
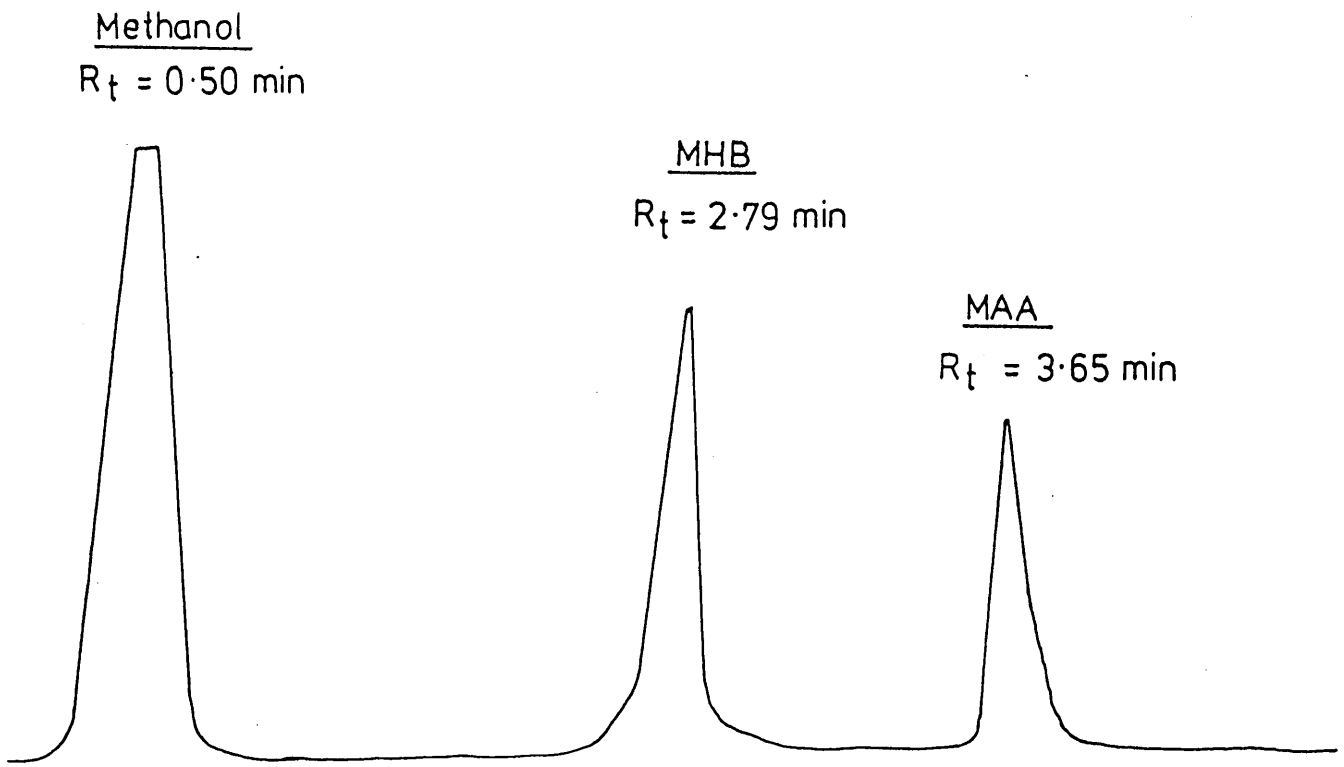


Figure 3.5.2 Gas Chromatogram of MAA/MHB Mixture in Methanol



of vacuum distillation were unsuccessful. Consequently, analysis for the enantiomeric composition of the MHB, produced during hydrogenation of MAA, was carried out while it remained in the reaction mixture.

This difficulty arose because of two factors concerning the structure of MHB:-

(i) The lack of success of attempts to separate MHB from solvents capable of hydrogen bond formation, for example, butanol, was probably due to their ability to form such bonds with the β-hydroxy group of MHB.

The apparently obvious answer to this problem was to use a solvent which was incapable of forming hydrogen bonds, such as toluene. However, the second factor then became important:-

(ii) As a result of MHB having the structure of a β-hydroxy ester, it had a strong tendency to dehydrate to form the corresponding enone, with a simultaneous loss of chiral centre:-

$$CH_3-\overset{*}{\underset{OH}{CH}}-CH_2-CO_2CH_3 \xrightarrow{-H_2O} CH_3-CH=CH-CO_2CH_3$$

It is known that, when toluene is distilled from a solution, it will combine with, and therefore remove, any water which happens to be present; in fact it was found that, with MHB dissolved in toluene, removal of the toluene by distillation promoted this unwanted dehydration reaction.

However, dehydration during solvent distillation

occurred even with solvents such as ethyl acetate and methyl propionate; this was most probably due to the presence of basic sites in the silica glass distillation apparatus - any acid or base present would behave as a catalyst for the dehydration reaction.

Since the dehydration of MHB could result in a change in its enantiomeric composition, it was important that no such reaction occurred prior to its analysis. Provided with the fact that this did not occur if no distillation was attempted, carrying out the analysis of MHB while it remained in the reaction mixture was found to be the most accurate procedure possible.

The method used for chiral analysis, as well as the alternatives which were considered will be discussed in Chapter 4; polarimetry was eventually chosen as the most suitable method.

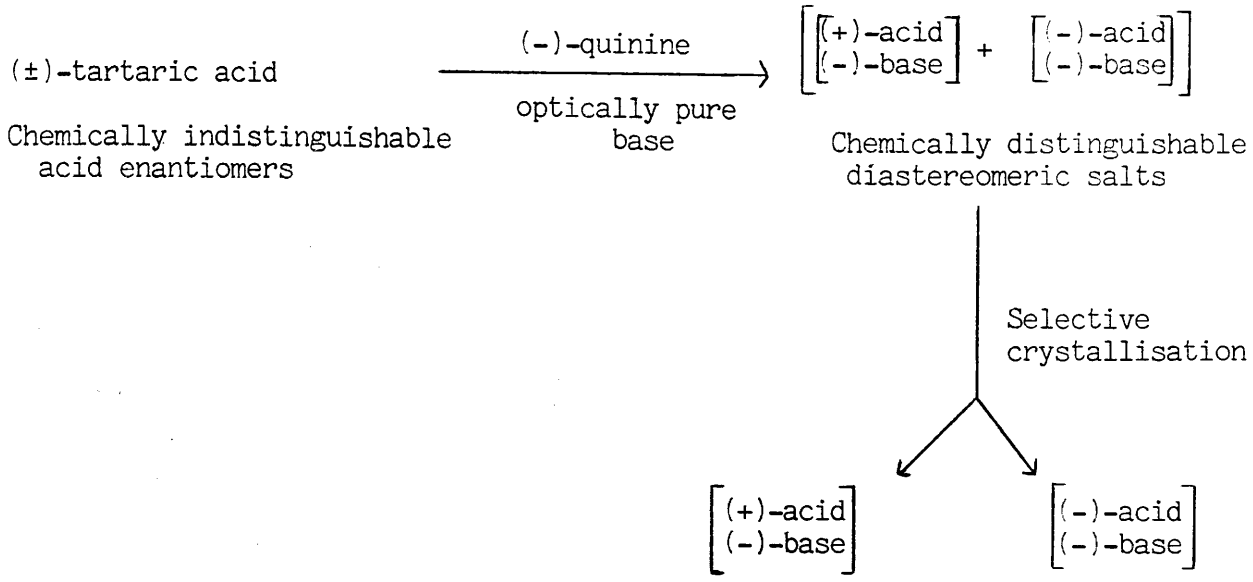
CHAPTER 4

PHYSICAL METHODS OF CHIRAL RECOGNITION

4.1 Introduction

In order to evaluate the chiral efficiency of any asymmetric synthesis, some means of chiral recognition is required, since the two enantiomers of a particular compound are chemically indistinguishable. Significant advances in the efficiency and range of asymmetric reactions which can be carried out have been made in recent years and it is of vital importance that the evaluation of the resulting enantiomeric ratios is achieved with a high degree of accuracy. In spite of this, however, relatively little progress has been made in the development of possible techniques for this purpose. In fact, with a few exceptions, the procedures recommended by Pasteur[122] a century ago are still predominantly employed.

In 1848 Pasteur, with the aid of a microscope, succeeded in separating the two types of crystals of sodium ammonium "racemate" by hand. At that time "racemic acid" was the name for racemic tartaric acid, while "tartaric acid" was that for the dextrorotatory enantiomer, which was obtained during the manufacture of wine. Unfortunately, however, only very few compounds could be resolved by this particular method and, in 1852, Pasteur found that "racemic acid" could be resolved with the aid of naturally occurring optically active bases, such as (-)-quinine. This process can be summarised in terms of more modern theory in the following way:-



Differences in solubility of the diastereomeric salts enabled selective crystallisation to be performed, and recovery of the acid enantiomers from the separated salts could be achieved without much difficulty.

It is perhaps interesting to note that Pasteur's achievements were made at a time when a proper understanding of asymmetry and asymmetric synthesis did not in fact exist![10]

In order for any technique to possess the ability to distinguish between the two enantiomers of a particular compound, there must be some source of chirality within the technique itself. In practice, such techniques can be separated into two distinct groups:-

(a) Initial reaction of enantiomers with some optically pure chiral agent, followed by separation of the resulting diastereomers.

In these cases the source of chirality is the optically pure agent; for example, the optically active base (-)-quinine was the source of chirality in Pasteur's

separation of diastereomeric salts.

(b) Direct chiral recognition of enantiomers.

In these cases the source of chirality is inherent in the technique itself. An example is polarimetry, where the source of chirality is the left and right circularly polarised components of plane polarised light.

Various methods of chiral recognition and their suitability for use in this project will now be discussed and compared.

4.2 Gas Chromatography.

There are several advantages in using gas chromatography as an analytical technique for optical yield determination:-

(i) only a very small sample size is required (around 10mg of solution).

(ii) the sample need not be 100% pure.

(iii) small changes in optical purity can be detected as a result of the high sensitivity of the technique.

(iv) this high sensitivity is independent of factors such as solvent, which are important in, for example, polarimetric measurements.

The basic requirement is that resolution of enantiomeric mixtures can be obtained and so a precise measurement of enantiomeric composition would involve a comparison of relative peak areas. In fact there exist, two, quite different, gas chromatographic techniques for this purpose:-

(1) conversion of the enantiomers into diastereomeric derivatives by chemical reaction with an auxiliary, enantiomerically pure, chiral agent and subsequent gas chromatographic separation of the resulting diastereomers on an achiral stationary phase.[123]

(2) direct resolution of the enantiomers on a chiral stationary phase,[124] that is, one which contains an auxiliary, enantiomerically pure, chiral agent.

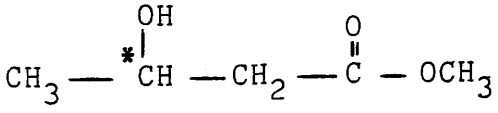
In principle, therefore, gas chromatography can be used as either a method of type (a) or (b) according to the classification in the previous section.

Since chromatographic conditions are specific for the material which is to be analysed, techniques (1) and (2), and their suitability for use in this work, will both be discussed in some detail.

4.2.1 Resolution of Derivatised Enantiomers on an Achiral Stationary Phase.

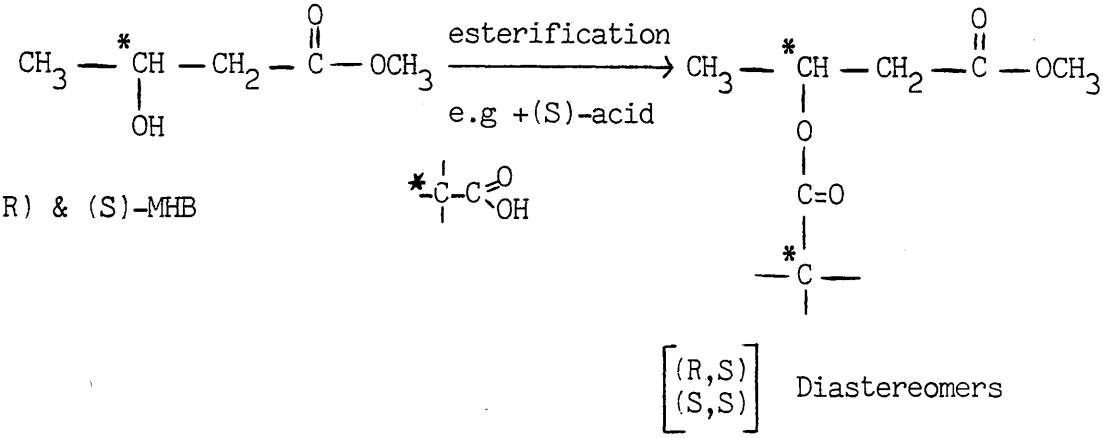
The fundamental requirement of the chiral substrate to be resolved is that it should possess at least one functional group for quantitative reaction with the chiral agent. The nature of the functional group, or groups, will determine which chiral agent will be effective.

Consider, therefore, the structure of MHB:-

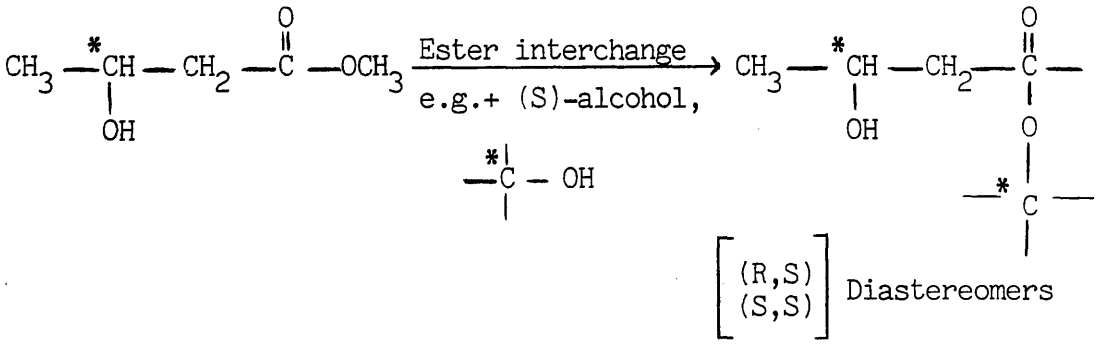


MHB has two functional groups and so there exist two possible methods of derivatisation:-

(i) via the -OH group and an esterification reaction:-



(ii) via the $-\overset{O}{\overset{\|}{C}}-OH_3$ group and an ester interchange reaction:-



There is one major difference between the two sets of diastereomers produced during reaction types (i) and (ii). In (ii), the two chiral centres are separated by $-(CH_2-\overset{O}{\overset{\|}{C}}-O)$ compared with only $-(\overset{O}{\overset{\|}{C}}-O-)$ in (i). It has, however, been shown that, as the distance between the chiral centres increases, there is a simultaneous decrease in resolution of the diastereomers.[125] For this reason, the esterification

process shown in (i) was chosen for the attempted derivatisations of MHB in preference to the ester interchange reaction scheme shown in (ii).

4.2.1.1. Acetylated Lactic Acid with MHB.

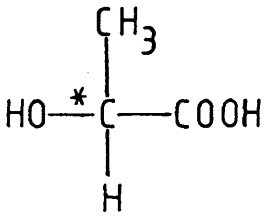
Acetylated (L)-(+)-lactic acid has been reported as a convenient derivatising agent for secondary alcohols.[125] The reaction pathway is shown in Figure 4.2.1.1.1; the acetylation step II results in the formation of α-acetoxy-propionates, which are generally better resolved than lactates with an unprotected hydroxy group.

I. MHB (2.60g, 0.022 moles) and (L)-(+)-lactic acid (2.25g, 0.025 moles) were refluxed overnight in benzene (10ml) while water produced during the reaction was removed with a Dean-Stark trap. After washing with saturated, aqueous sodium hydrogen carbonate solution and drying over anhydrous sodium sulphate, the solvent was removed by distillation.

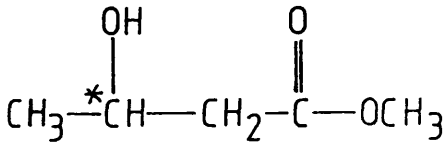
II. Acetic anhydride was refluxed with an equimolar amount of the ester from I for 5 hours in dibutyl ether. Acetic acid and dibutyl ether were then removed at atmospheric pressure and the product obtained by distillation.

Gas chromatography of 10 µℓ samples was carried out on a 10' long, 1/4" o.d. stainless steel column packed with a 20% W/W dispersion of 1,2,3 tris(2-cyanoethoxy propane) supported on 60-80 AW Chromosorb P DCMS.

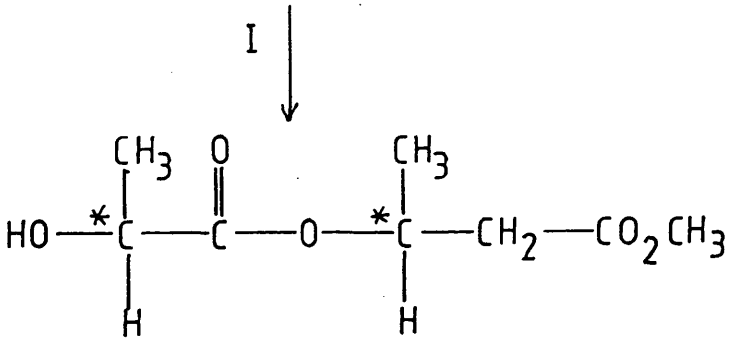
Figure 4.2.1.1.1 Derivatisation of MHB with L-(+)-Lactic Acid

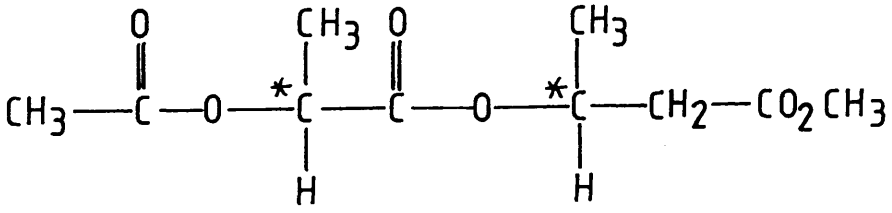


L-(+)-Lactic acid



(R)- and (S)-MHB





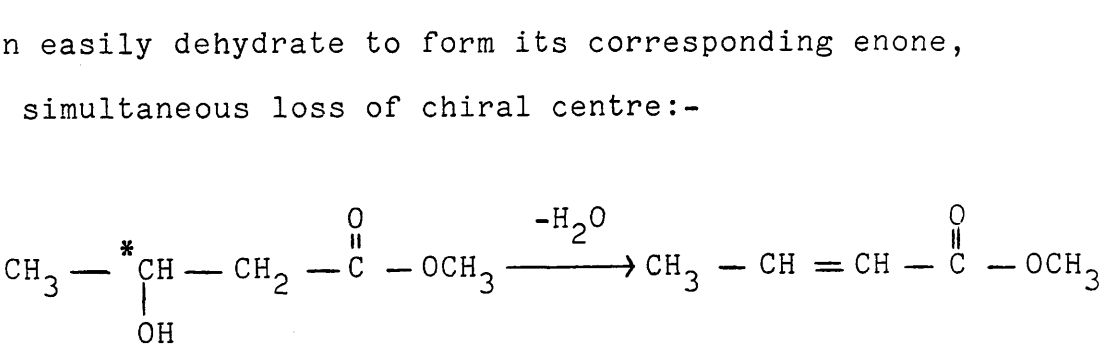
[(S,R) (S,S)] Diastereomers

Figure 4.2.1.1.2 shows the chromatogram obtained after stage I; the peak of retention time 125 min. was tentatively assigned to the diastereomeric lactate esters, while its considerable width could have been due either to:-

(a) its retention time - peak width is known to increase with retention time, or

(b) the presence of two, unresolved peaks, one for each diastereomer, which might have been resolved after carrying out stage II of the reaction. The obvious problem was the incomplete reaction of MHB, the presence of which was evident from the extremely large peak of retention time 70 min. Enantiomeric composition can be accurately determined in this way only if the esterification reaction proceeds to completion.

The main difficulty in esterifying MHB becomes apparent on a closer examination of its structure, which is that of a β-hydroxy ester. Even under very mild conditions, MHB can easily dehydrate to form its corresponding enone, with a simultaneous loss of chiral centre:-

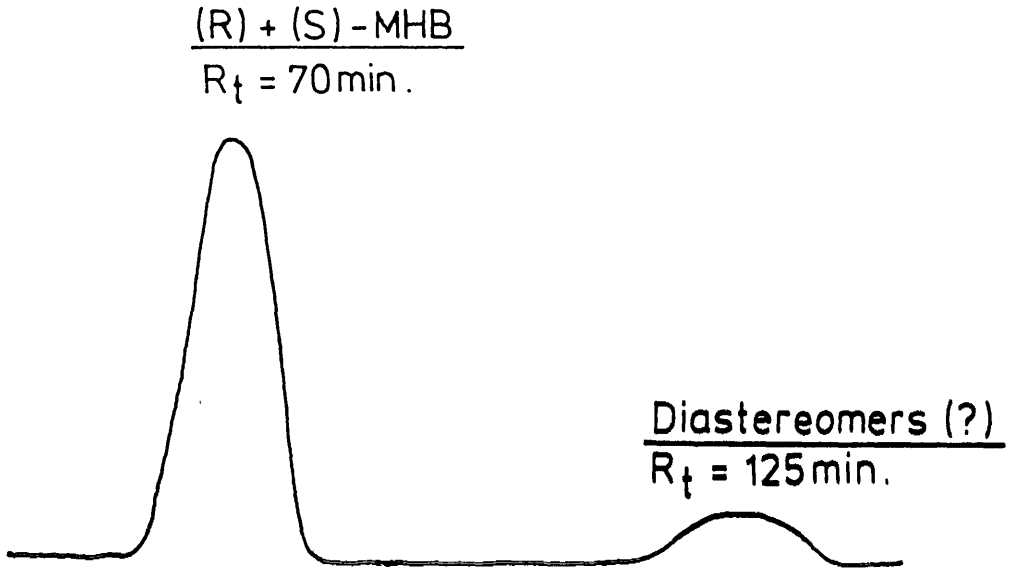


MHB

Since the presence of any H^+ (or OH) ions would promote this dehydration reaction, it was not possible to include an acid catalyst in the attempted esterification of MHB. Instead, the presence of lactic acid provided a means by which self-catalysed esterification could occur.

Figure 4.2.1.1.2 Gas Chromatogram of Racemic MHB after Reaction with L-(+)-Lactic Acid

Column Temperature = 125°C (isothermal)
Carrier Gas (N_2) Flowrate = 90 ml/min



In an effort to improve the efficiency of the esterification reaction, an alternative approach was next considered.

4.2.1.2. Chrysanthemoyl Chloride with MHB

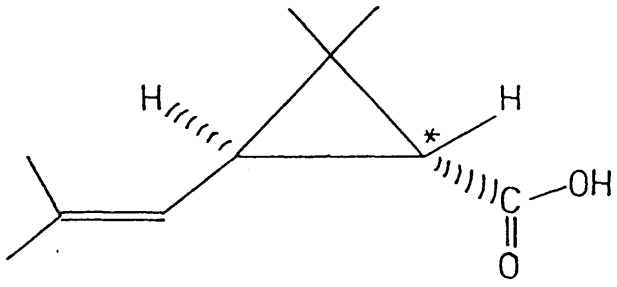
It is generally accepted that acid chlorides are usually more reactive than carboxylic acids towards alcohols. Chrysanthemoyl chloride, a monoterpenoid, is known to react smoothly with a variety of secondary alcohols[126] and the reaction scheme with MHB is shown in Figure 4.2.1.2, starting with chrysanthemic acid.

I. (R)-(+)-trans-chrysanthemic acid (15 µℓ, 9.7 x 10^{-5}mol) in dry, redistilled toluene (0.5ml) was treated with thionyl chloride (1.1ml, 1.5 x 10^{-2}mol) at 60°C for 1 hour. Excess thionyl chloride and solvent were then removed in a stream of nitrogen and the acid chloride dissolved in toluene (150 µℓ) for immediate use, without further purification.

II. The acid chloride solution from I was treated with MHB (4 µℓ, 3.6 x 10^{-5}mol) in toluene (70µℓ), and a few drops of triethylamine added for catalytic purposes. After two hours at room temperature, most of the solvent was removed in a stream of nitrogen.

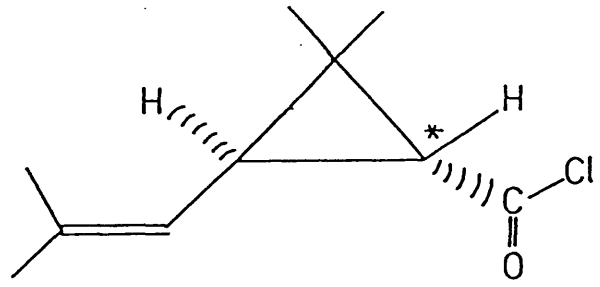
Gas chromatography of 10 µℓ samples was carried out on a 10' long, 1/4" o.d. stainless steel column, packed with a 15% W/W dispersion of UCON fluid supported on 60 - 80

Figure 4.2.1.2 Derivatisation of MHB with (R)-(+)-trans-Chrysanthemoyl Chloride



(R)-(+)-trans-chrysanthemic acid

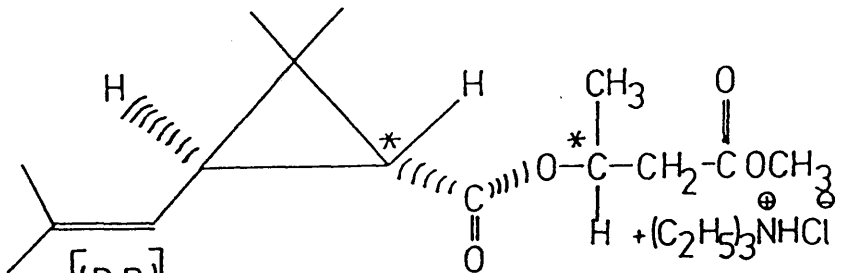
I ↓ + $SOCl_2$, thionyl chloride



(R)-trans-chrysanthemoyl chloride

II ↓ + $CH_3^*CH(OH)CH_2CO_2CH_3$ + $(C_2H_5)_3N$

(R)- and (S)- MHB



[(R,R) (S,S)] Diastereomers

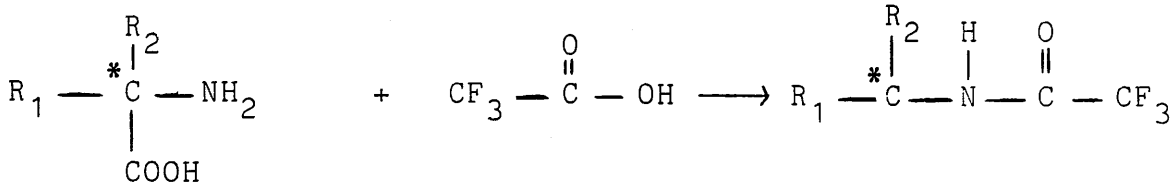
Chromosorb W. However, gas chromatograms of samples after stage II were almost identical to that shown in Figure 4.2.1.1.2 - that is, MHB had again failed to react to any appreciable extent. Thus, it was obvious that neither was this derivatisation procedure a suitable means of resolving the enantiomers of MHB.

Since the susceptibility of MHB to dehydration prevented the use of acid catalysts in any esterification process, and thus the determination of its enantiomeric composition by the formation of diastereomers, attention was then focussed on possible methods of direct resolution.

4.2.2 Resolution of Enantiomers on a Chiral Stationary Phase.

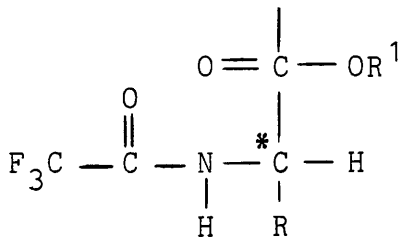
This method also depends on the formation of diastereomers for resolution of optically active substances, in that resolution is achieved via the rapid and reversible diastereomeric interaction between the substance and the optically active stationary phase. In fact, this method is more attractive for the determination of enantiomeric composition than that described in Section 4.2.1. since it excludes the possibility of accidental alterations in the original ratio of enantiomers during, for example, chemical or physical manipulations of the optically active material. A further advantage is that the optically active material, if produced by some asymmetric synthesis, may be analysed without isolation and purification, provided the analysis does not require sample derivatisation. Such a derivatisation with some achiral substance is, however, necessary for non-

volatile or highly polar substances, or, alternatively, for the introduction of suitable groups, in order to improve resolvability. The resolution of many amino acids, for example, is greatly improved by the addition of a trifluoroacetyl group:-[127]



CHIRAL Amino Acid (R_1, R_2 alkyl) | ACHIRAL trifluoro acetic acid | N-Trifluoroacetyl amino acid ester

The first successful resolution of enantiomers was, in fact, of amino acids derivatised in this way, using the chiral stationary phase N-trifluoroacetyl-L-isoleucine lauryl ester:-[128]

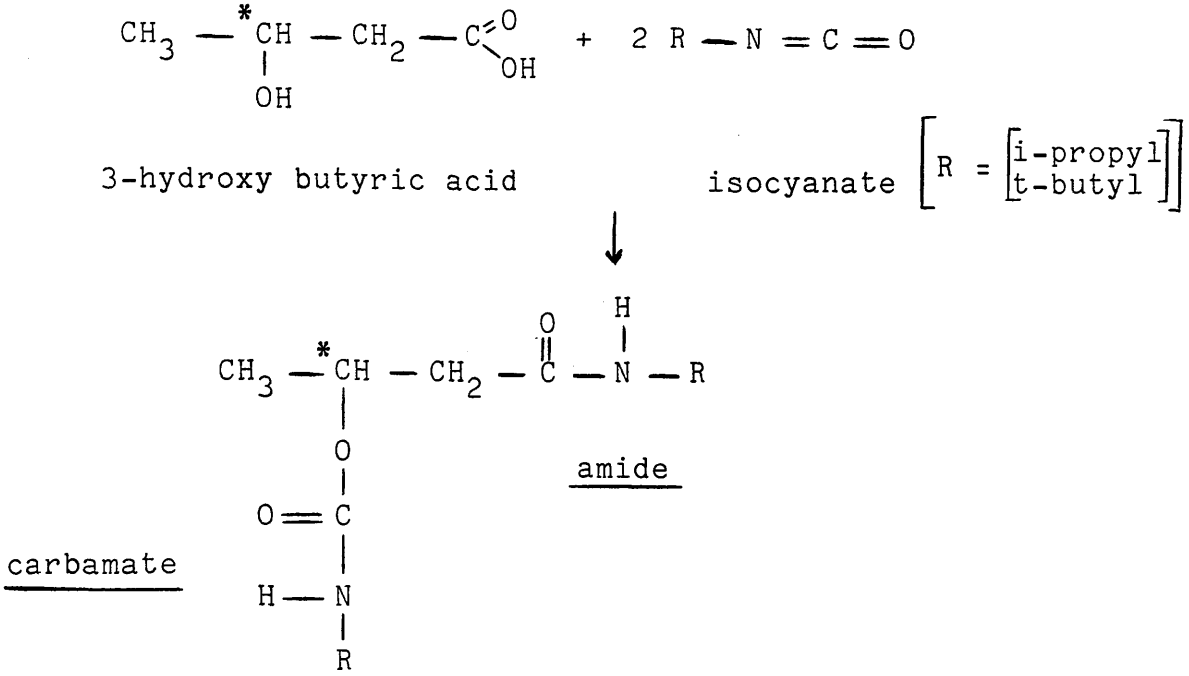


Great improvements in the thermal stability of such phases have since been made, for example by coupling the chiral ester unit to some copolymer <u>via</u> the amino groups. The resolving ability has also been improved by the presence of additional N-H groups, which can participate in the process of chiral recognition by means of hydrogen bonding.

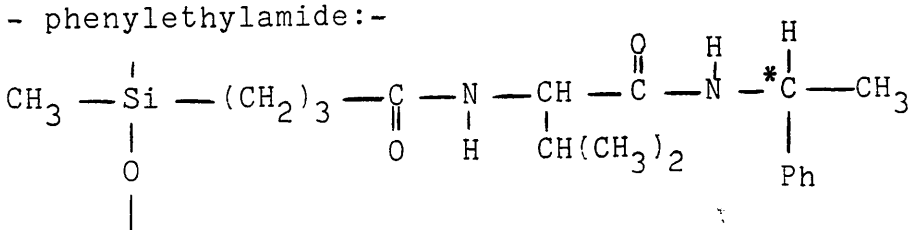
Resolution of α-hydroxy acids and their esters

has been possible for some time,[129] while that of β-hydroxy acids has also now been achieved.[130] Derivatisation of the latter group of acids with an isocyanate is, however, necessary; this process is illustrated in Figure 4.2.2.1:-

Figure 4.2.2.1



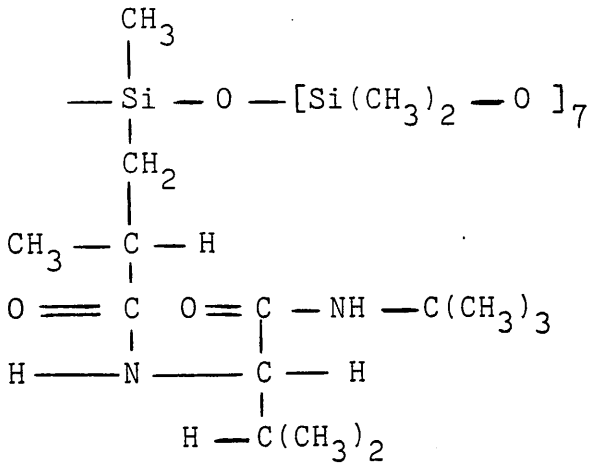
The reaction of two isocyanate molecules with one acid molecule resulted in the production of both an amide and a carbamate group, that is, both the -OH and -COOH functions of the hydroxy-acid were derivatised. These two —(N — C —) groups then behaved as binding points to the chiral phase and separation of these derivatised enantiomers was possible using the stationary phase XE - 60 - (L) - valine - (S) - α - phenylethylamide:-



However, the successful resolution of enantiomers of β-hydroxy esters had yet to be reported. Nonetheless, some attempt was made to resolve the enantiomers of MHB using a chiral stationary phase.

4.2.2.1 Attempts using Underivatised MHB.

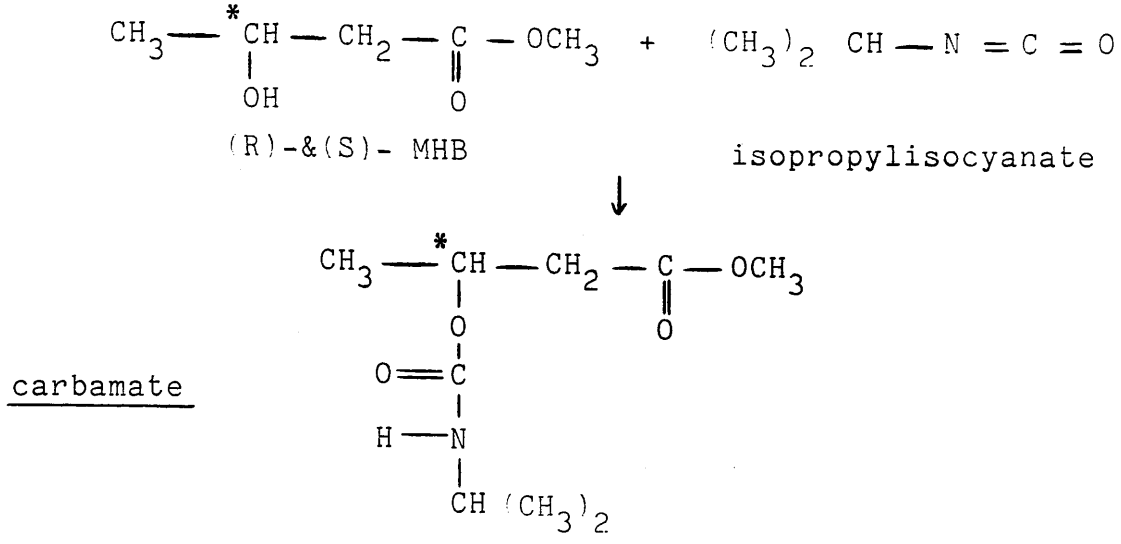
First of all, gas chromatography of samples containing both (R)- and (S)-MHB was carried out using the chiral stationary phase Chirasil-(L)-val, which was available commercially. The structure of this phase is:-



However, no resolution of the two enantiomers was observed.

4.2.2.2 Attempts using Derivatised MHB

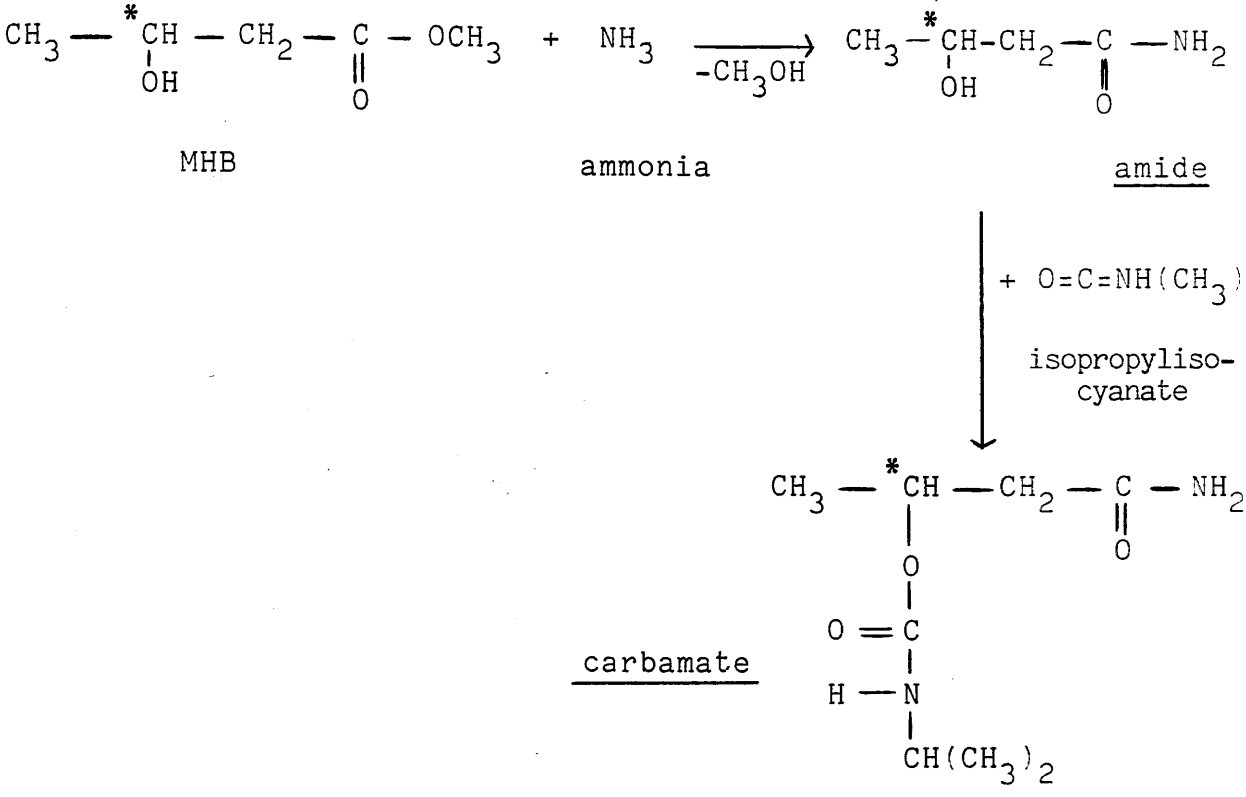
MHB was then derivatised by reaction with iso-propylisocyanate:-



This derivatisation was achieved by heating an enantiomeric mixture of MHB (100 µg) with isopropylisocyanate (150 µℓ) in dichloromethane (150 µℓ) at 100°C for one hour, after which time excess isocyanate and solvent were removed in a stream of nitrogen. Gas chromatography of the remaining species showed that the derivatisation of MHB had indeed been completed.

Although the derivatisation process had been successful, however, there was no subsequent chromatographic resolution of the carbamate enantiomers using Chirosil-(L)-val as the stationary phase. This failure was attributed to the availability of only one functional group in MHB for reaction with the isocyanate - this was in contrast to the situation with β-hydroxy acids, where, as was shown in Figure 4.2.2.1, both the -OH and -COOH groups were derivatised to form two $-(\overset{H}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-)$ linkages per acid molecule. It was therefore evident that at least two peptide linkages per molecule were required if the two enantiomers were to be resolved using this technique.

If it were possible to carry out some sort of ammonolysis reaction of the ester group in MHB to produce the second vital peptide bond, it would seem highly probable that the resulting doubly derivatised enantiomers could be resolved:-



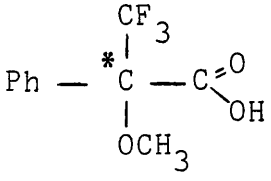
Unfortunately, there is a strong possibility that the ammonolysis step would involve the racemisation, and perhaps dehydration, of MHB, thus rendering the technique useless. In view of the extreme difficulties encountered during these attempts involving chiral stationary phases, it had become apparent that the resolution of the enantiomers of MHB by means of this method was a task requiring resources beyond those available during this project.

4.3 Nuclear Magnetic Resonance Spectroscopy.

The basic requirement for the determination of enantiomeric composition by nmr spectroscopy is a means of chiral recognition which allows, for example, proton resonances for different enantiomers to occur at different frequencies. Several methods are available for this purpose, such as chiral shift[131] and chiral solvating agents.[132] Chiral shift reagents in particular can often result in line broadening and hence the loss of the enantiomeric resolution which was desired to be produced. For this reason, an extremely convenient method for resolving enantiomeric alcohol molecules which avoids the use of such shift or solvating agents has been developed.

4.3.1 MHB with a Chiral Derivatising Agent.

The optically active acid α-methoxytrifluoromethylphenylacetic acid, MTPA, which has the structure



and is known as Mosher's Reagent, can react with enantiomeric alcohol molecules to form diastereomers, which are chemically distinguishable by nmr.[133] Furthermore, the presence of the fluorine atoms allows the use of ^{19}F nmr spectroscopy, which has the advantage that the difference in chemical shift of the ^{19}F signals of the two diastereomers is greater than

that for protons and so there is absolutely no requirement for an additional shift reagent. The derivatisation of MHB with (S)-MTPA was a two-stage process and is outlined in Figure 4.3.1.1.

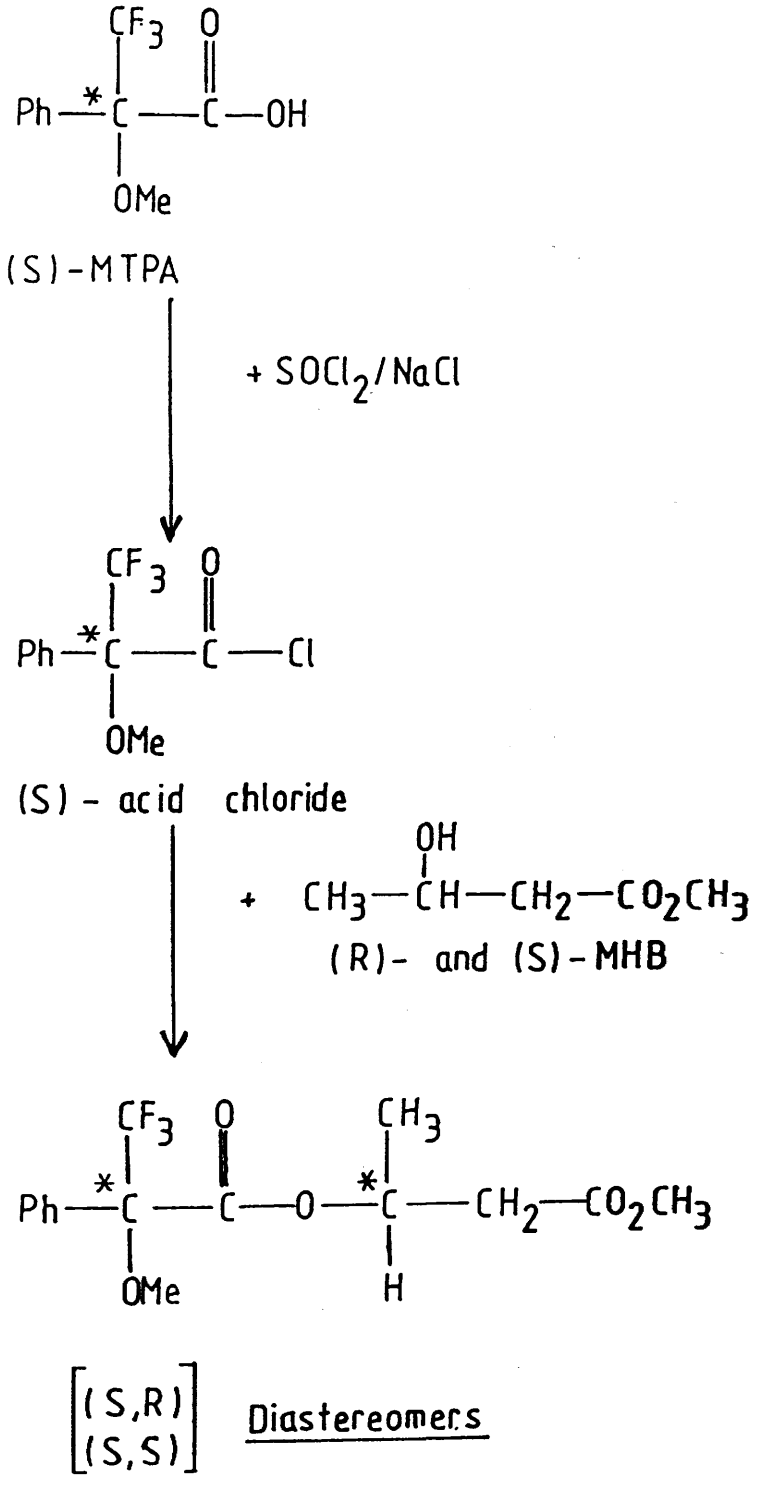
I. (S)-MPTA (2.00g, 6.35×10^{-3}mol) and sodium chloride (0.02g, 4.15×10^{-4}mol) were dissolved in thionyl chloride (4.4ml) and refluxed for 50 hours, after which time the excess thionyl chloride was removed by the process of vacuum distillation; (S)-MTPA was thus converted to its corresponding acid chloride, which was preferable to MTPA itself for the purpose of reaction with MHB.

II. MHB (0.18g, 1.52×10^{-3}mol (R)- + 0.06g, 5.1×10^{-4}mol (S)-MHB) was dissolved in dry diethyl ether (15ml) and several drops of pyridine added. The chloride from (I) was slowly added to this mixture and the resulting solution left overnight at room temperature. After washing with cold, dilute hydrochloric acid (3 x 20ml), saturated sodium carbonate (3 x 20ml) and sodium chloride aqueous solutions (3 x 20ml), the solution containing the product mixture was dried over anhydrous magnesium sulphate and the ether subsequently removed.

The ^{1}H and ^{19}F nmr spectra of the product mixture are shown in Figures 4.3.1.2 and 4.3.1.3 respectively.

The ^{1}H nmr spectrum was rather complex and not particularly informative. This was not surprising; since the immediate surroundings of each proton type were so

Figure 4.3.1.1 Derivatisation of MHB with (S)-MTPA



[(S,R) (S,S)] Diastereomers

Figure 4.3.1.2 100MHz ^{1}Hnmr Spectrum of [MTPA Chloride + (R)- and (S)- MHB]

(Reference :- TMS ; Solvent :- $CDCl_3$)

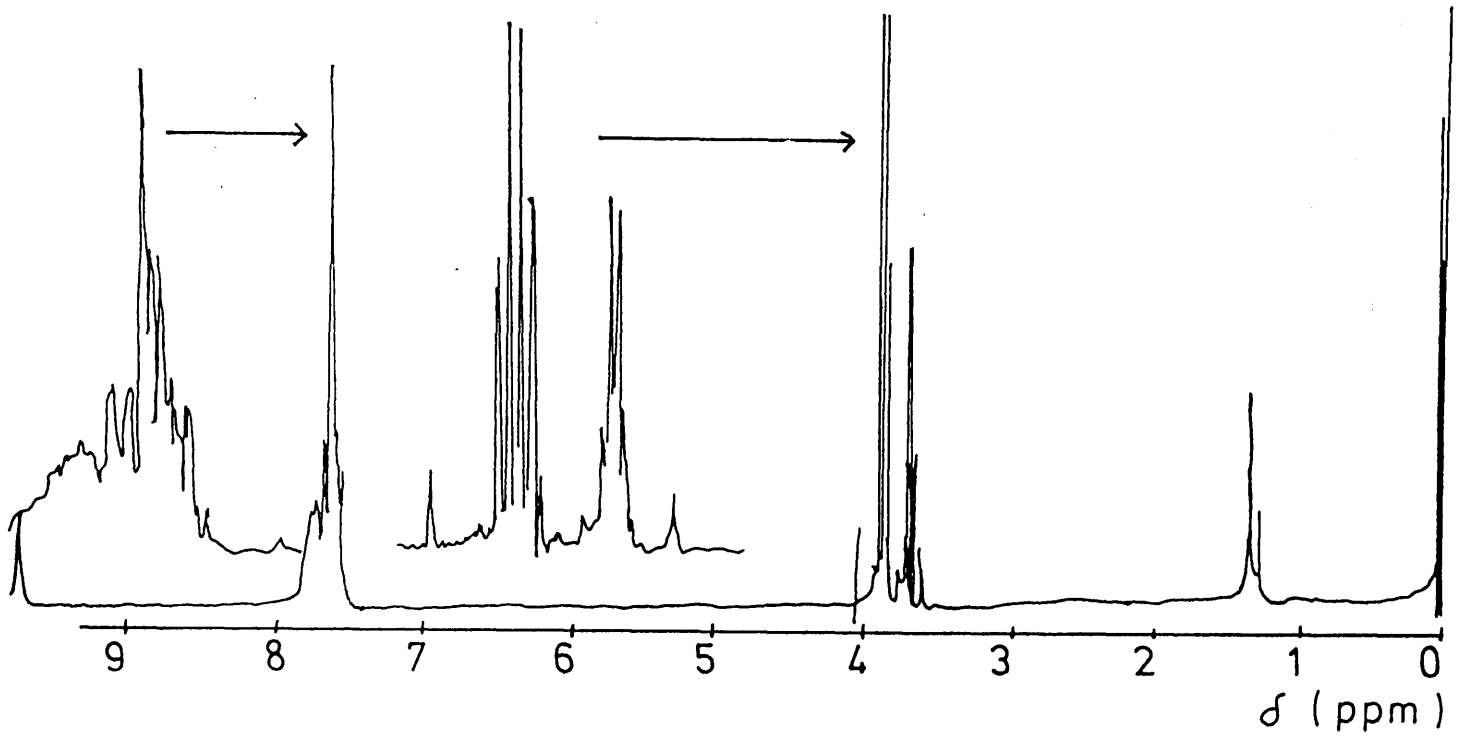
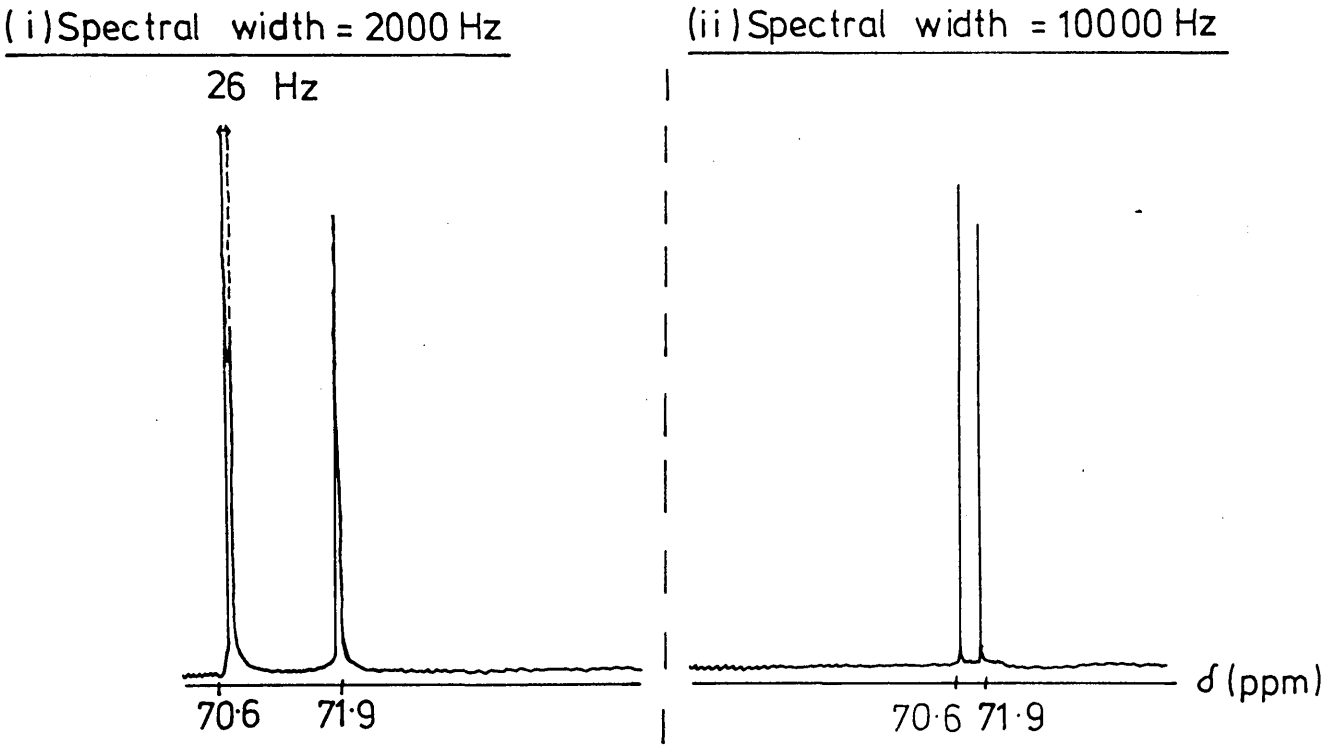


Figure 4.3.1.3 ^{19}F nmr Spectra of [MTPA Chloride + (R)- and (S) - MHB]

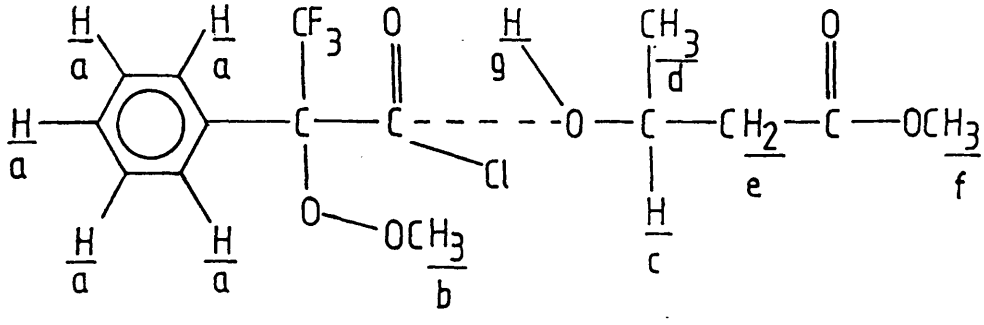
(Reference :- TMS ; Solvent :- $CDCl_3$; ^1H decoupled, 100 MHz spectra)



similar in the ester product in comparison with those in the starting materials, the signals had the tendency to overlap. The approximate chemical shifts are shown in Table 4.3.1.1.

Table 4.3.1.1.

Proton(s)	a	b	c	d	e	f	g
Chemical shift(ppm)	7.5	3.6	4.2*	1.3	2.4	3.6	3.4



Consequently, the only conclusion which could be made from Figure 4.3.1.2 was that a mixture of acid chloride, MHB and ester products was present; the presence of MHB which had not been esterified with the acid chloride was evident from the relatively broad signal due to H_g - that is, the proton signal of the alcohol group.

In theory, the ^{19}F nmr spectrum should be more helpful, since the separation of the signals for the acid chloride of MTPA and its esters with MHB should be greater than those for the protons. Spectrum (ii) in Figure 4.3.1.3 consisted of two peaks only, at δ values of 70.56 and 71.95 ppm respectively. However, by decreasing the spectral width from 10000 to 2000 Hz per 25mm, it was observed that

the 'peak' at around 70.5 ppm was beginning to be resolved into two, the details of Spectrum (i) are shown in Table 4.3.1.2

Table 4.3.1.2

Chemical shift (ppm)	70.554	70.588	71.947
Relative Peak Area (Arbitrary Units)	209	132	149

It was known that none of the three ^{19}F signals was caused by the presence of unreacted MTPA itself and so it was apparent that, while the signal of chemical shift 71.947 ppm must have been due to traces of unreacted acid chloride, the two peaks of shift 70.554 and 70.588 ppm respectively could be attributed to the two, chemically different, diastereomers shown in Figure 4.3.1.1. Thus, the desired resolution had been obtained, if only to a small extent. Although this finding was extremely encouraging, the inescapable fact was that, once again, the reaction of MHB with the optically pure derivatising agent had failed to proceed to completion. As a result, it had to be conceded that this technique was not suitable for the purpose of determining the enantiomeric composition of MHB and so attention was then focussed on polarimetric methods.

4.4. Polarimetry

4.4.1 The Nature of Light and Origin of Optical Activity

Light can be described as a transverse wave of

alternating electromagnetic field, obtained as a solution of Maxwell's Equations, and is a type of electromagnetic wave. Linearly polarised light consists of two, right and left circularly polarised components, which, together, behave as a propagative wave, travelling in one plane. For example, Figure 4.4.1 (i) is a representation of light which is linearly polarised in the direction of the z axis.

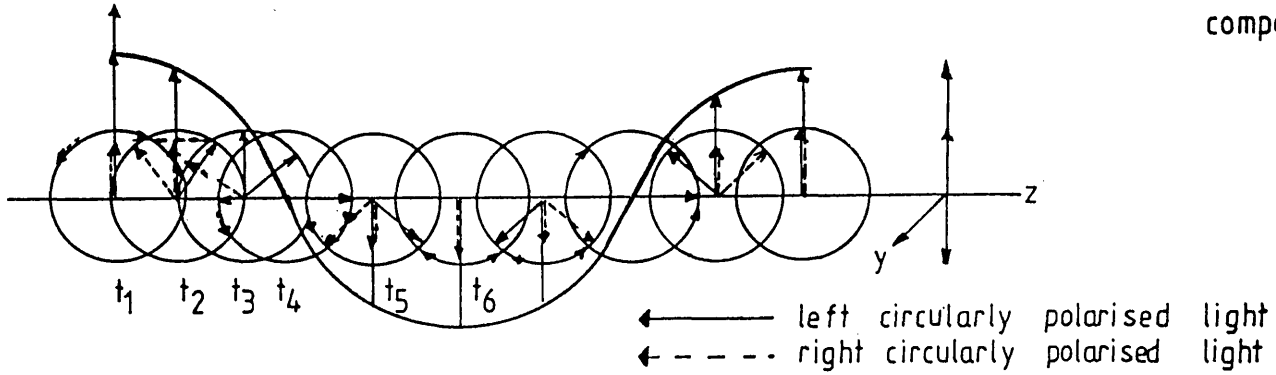
When light passes from one medium to another, its direction of propagation is altered and so, also, is its velocity. This phenomenon of bending at a boundary is called refraction, the degree of which is described by the refractive index. Since the velocity of light reaches a maximum, c, in a vacuum ($c = 3 \times 10^8 ms^{-1}$) the refractive index of a vacuum is taken as a standard. The refractive index, n, for a particular medium is therefore

$$n = \frac{c}{v} \qquad (4.4.1.1)$$

where v is the velocity of light in the particular medium. When linearly polarised light passes through a material which has different refractive indices for the left and right circularly polarised components, n_l and n_r, respectively, this light will be split into left and right circularly polarised beams, which will propagate with different velocities. When this occurs, the vibrational plane changes, a phenomenon known as optical rotation, and this effect is shown in Figure 4.4.1(ii). Any material which causes this optical rotation is said to be optically active. Consequently, optical

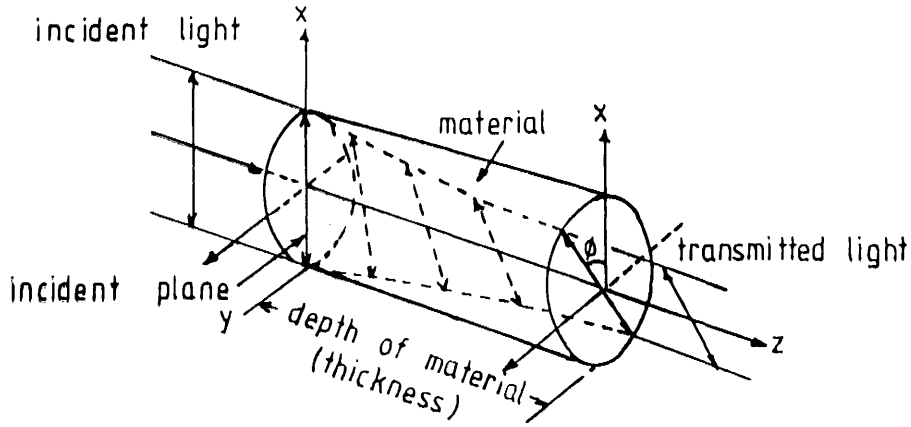
Figure 4.4.1

(i) Linearly polarised light as a combination of left and right circularly polarised components.



(circles represent circular polarisation vectors in xy plane for time $t_1 \rightarrow t_6$)

(ii) Representation of phenomenon of optical rotation (for a laevorotatory material, $n_r > n_l$.)



activity is observed if a material has unequal refractive indices for left and right circularly polarised light.

The observed angle of rotation, α, is related to that per unit concentration of material per unit length, $[\alpha]$, called the relative specific rotation, by the expression

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l\,[c]} \qquad (4.4.1.2)$$

where $[c]$ is the concentration of sample (gml^{-1})

l is the path length of the sample cell (dm)

T is the temperature at which measurements are made (^{o}C)

λ is the wavelength of light, the plane of polarisation of which is being rotated.

Angles of rotation are normally measured using a polarimeter.

4.4.2 The Polarimeter

In 1812, the first observation of an alteration in the plane of polarisation of linearly polarised light was made by J.B. Biot[134] when a linearly polarised beam entered a sample of quartz from the direction of an optical axis, he noticed a clockwise rotation, with respect to the direction of propagation, in dextro-quartz and, in contrast, an anticlockwise rotation in laevo-quartz. The specification of instruments available today are in fact based largely on parameters developed by Biot in the years following his first observations.

In the present work an AA - 10 automatic digital polarimeter (Optical Activity Ltd) was used, which is illustrated schematically in Figure 4.4.2.

4.4.3 Method of Measurement of Optical Rotation Angles.

All measurements were made at 20°C, with a monochromatic light source of wavelength 589nm, the D-line in the emission spectrum of sodium; this wavelength of light was chosen so that no absorption by any sample would occur. The polarimeter cell used throughout was of capacity 1ml and path length 1dm.

The digital display was set to zero with the cell filled with solvent. The cell was then washed with acetone and thoroughly dried. A solution of the chiral material was carefully added to the cell and the optical rotation, α, noted; the concentration of the material was around 20mg(ml^{-1}) in each case.

There are, undoubtedly, several disadvantages in using polarimetry as an analytical technique instead of, for example gas chromatography:-

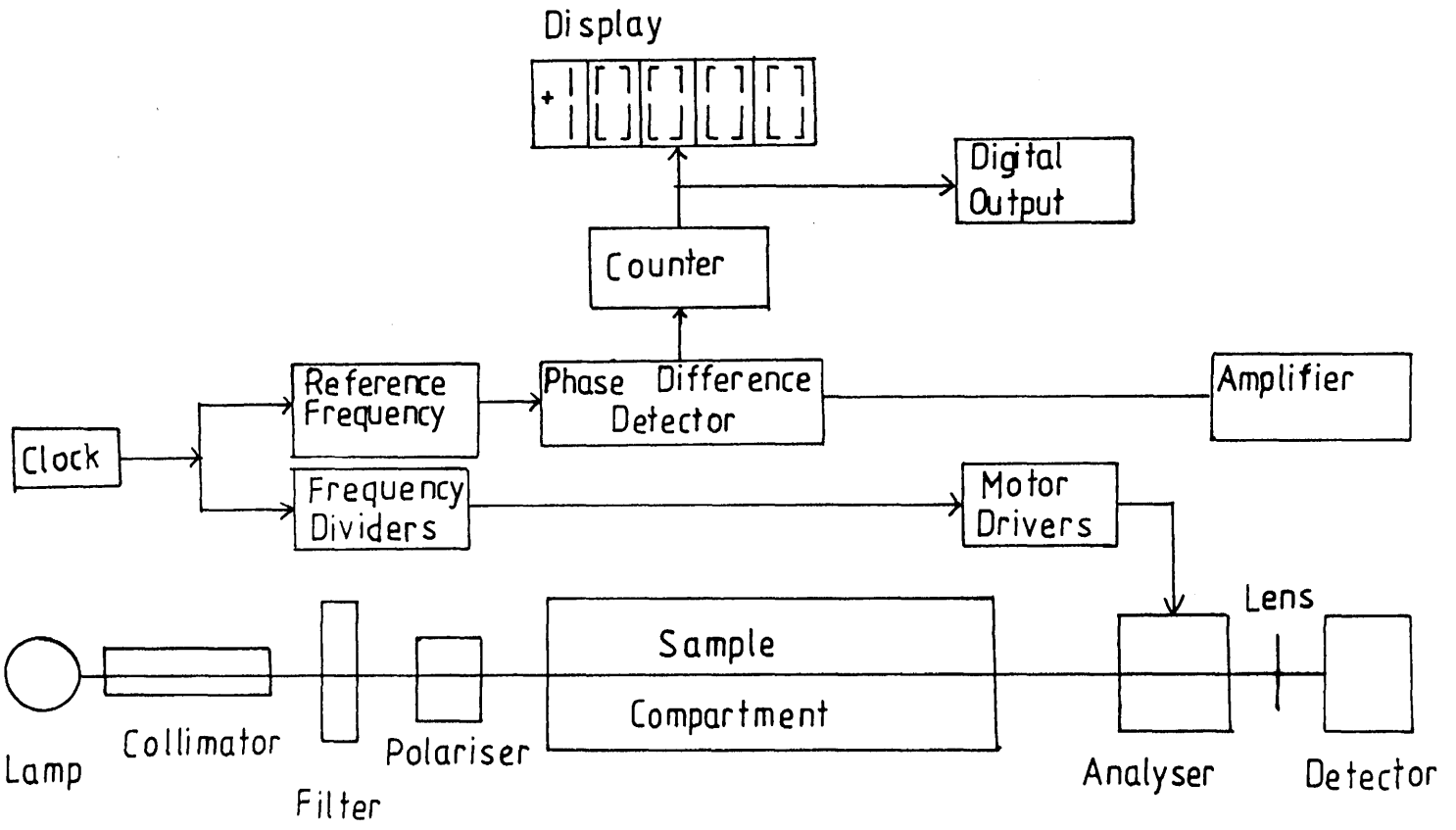
(a) Values of optical rotation are dependent on factors such as temperature and solvent

(b) If $[\alpha]_{\lambda}^{T}$ is small it can be difficult to detect small changes in optical purity.

(c) the sample must be pure

(d) Relative to chromatographic techniques, a large amount of sample is required; concentrations of solutions in a cell of path length 1dm must be no less than 10mg(ml^{-1}).

Figure 4.4.2 AA - 10 Automatic Digital Polarimeter



The two factors which were found to be the most important in this work were (a) and (c); in particular, the effect of solvent was found to be very large. Consequently, careful calibrations were required to allow for the solvent in which the chiral species were contained.

Despite these disadvantages, polarimetry was the only technique which could be used with confidence for the determination of the enantiomeric composition of MHB. This is perhaps reflected in the fact that all previous studies on asymmetric hydrogenation published by other research workers had used polarimetry, despite great advances in the other techniques described in this chapter over the last twenty years in particular. The exact method of determining enantiomeric excesses from polarimetric measurements is described in detail in Section 5.2.

4.5 Recent Developments

Since the experiments described in Section 4.2 and 4.3 were carried out, several significant developments have been made in the techniques of ^{1}H nmr spectroscopy and gas chromatography. Finally, some encouraging results have also been obtained from exploratory investigations using High Performance Liquid Chromatography.

4.5.1 ^{1}H nmr Spectroscopy

4.5.1.1 Shift Reagents in nmr Spectroscopy.

The fact that chiral shift reagents can be used as a means of chiral recognition in nmr spectroscopy has already been mentioned in Section 4.2; the point was also made, however, that a major disadvantage involved with the use of such a reagent is its broadening influence on the proton resonance signals which are to be studied. In spite of this, some investigations using a chiral shift reagent have recently been made, following a report which has recently been published on the subject of β-hydroxy esters.

The basic property of any shift reagent used in nmr spectroscopy, regardless of whether it is chiral or achiral, is that it possesses the ability to spread out, and therefore simplify, proton magnetic resonance spectra. The most common shift reagents are complexes formed between lanthanide metal ions, La, and 1,3 diketone ligands:-

$$La\left[R-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-R^1\right]_3 \qquad (R,R^1 = \text{alkyl})$$

This hexacoordinate complex is a Lewis acid and so is capable of forming weak addition complexes with a variety of organic bases, such as alcohols. The lanthanide metal ion thus becomes hepta-coordinated and it is this process which results in the spreading out, or shifting, of the proton signals. The magnitude of the induced downfield shift for each type of proton, $\Delta\delta$, is given by the McConnell

equation, in the derivation of which it is assumed that the heptacoordinate complex is axially symmetric:-

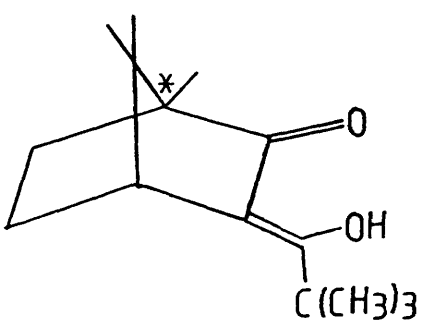
$$\Delta\delta = k\,(1-3\cos^2\theta)r^{-3} \qquad (4.5.1.1)$$

where k is a constant

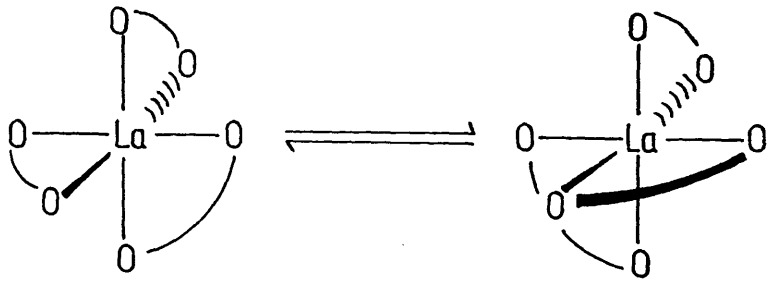
r is the distance between the nucleus and

θ is the angle formed between the particular nucleus and the axial axis of symmetry.

However, this is only an approximate relationship, since the complex may not be truly axially symmetric and there may be some shift mechanism occurring which is additional to the one accounted for. It is therefore fortunate that any doubts regarding the accuracy of equation 4.5.1.1 are only of minor importance when chiral shift reagents are used; this is because the major application of these compounds depends only on their capacity to effect different induced shifts for protons in different stereochemical environments. The first report of such an achievement appeared in 1970, following Whitesides and Lewis' investigations into the effect on the proton resonance signals of optically active alcohols and amines by adding small amounts of the complex $Eu(pvc)_3$, where pvc was the optically active ligand 3-pivaloyl-d-camphor:-[135]



The presence of chiral ligands, however, is not fundamentally required, since every hexacoordinate lanthanide complex of a diketone is itself chiral. Interconversion of the two enantiomeric forms is normally rapid:-



Δ - isomer Λ - isomer

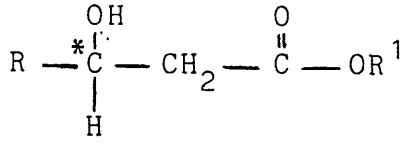
If the diketone is not symmetrically substituted, there will also be a pair of cis- and trans- isomers in both series. The situation becomes even more complex if the diketone is itself chiral; the chiral shift reagent derived from this type of ligand consists of four, rapidly interconverting chiral diastereomers - cis -Ω, cis - Δ, trans - Ω and trans-Δ. However, a detailed knowledge of the various isomeric structures, as well as their corresponding donor sites, is not necessary for the practical use of chiral shift reagents. The most effective shift reagents consist of a lanthanide metal, such as europium or ytterbium, coordinated to ligands which have a camphor-based structure.

The precise mechanism of action has yet to be fully understood, although several have been proposed. However,

the single conclusion that has been drawn from all the data available on chiral shift reagents is that the magnitude of the induced shift reflects a complex composite of mechanisms, all of which are based on the formation of diastereomeric complexes between the shift reagent and the enantiomers of the chiral species being studied.[136]

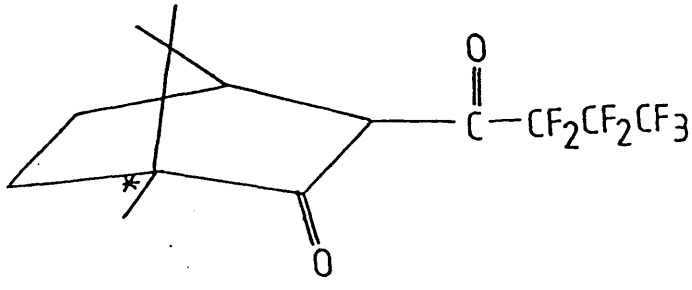
4.5.1.2 MHB with $Eu(hfc)_3$

Lipkowitz and Mooney[137] have recently reported a novel technique for the analysis of β-hydroxy esters of the type



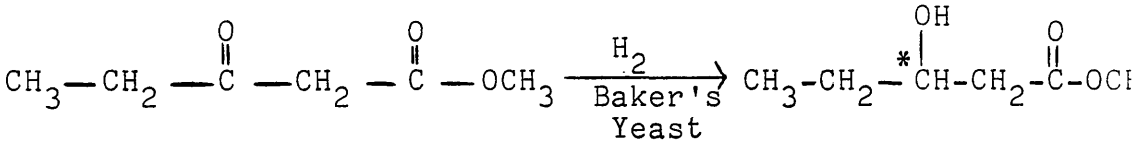
(R = Me, Ph, t-butyl;
R^1 = Me, Et, i-pr, t-butyl)

which involved using ^1H nmr spectroscopy in conjunction with the chiral shift reagent tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorato]-europium III, $Eu(hfc)_3$. Thus, the diketone ligand in this complex is itself chiral:-



In particular, the resolution of the proton signals for (R)- and (S)- ethyl 3-hydroxy butyrate (that is, the case where R = $-CH_3$, R^1 = $-CH_2CH_3$) which was obtained by adding a small amount of shift reagent to a solution of the ester in carbon tetrachloride was shown in some detail. Despite the broadening of signals which occurred as a direct consequence of the presence of the shift reagent, the authors claimed that

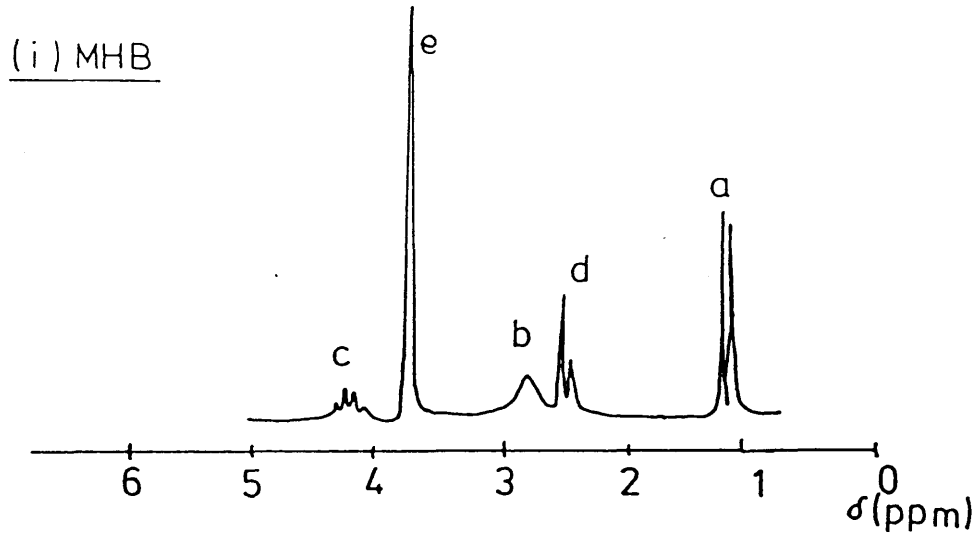
it was possible to determine the enantiomeric composition of the β-hydroxy ester in this way. The purpose of this analysis was to evaluate the chiral efficiency of the reduction of β-keto esters using baker's yeast. Because of its low cost and ready availability, baker's yeast is often used as a chiral reducing agent in the conversion of 3-oxo-alkanoic acid derivatives to the corresponding 3-hydroxy species.[138] An excess of the (R)-alcohol is always obtained, although not necessarily in a high optical yield. Nakamaru and co-workers[139] have recently reported an improvement in optical yields on including a small amount of an allylic alcohol in reaction mixtures, for example, in the reaction

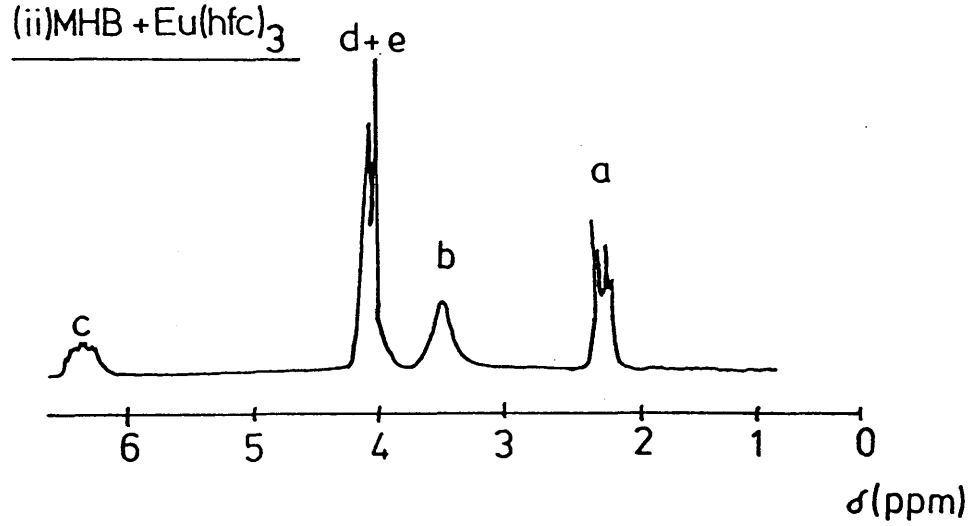


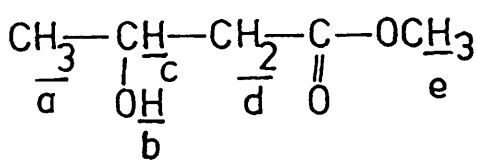
the enantiomeric excess was raised from 59 to 96%.

The effect of $Eu(hfc)_3$ on the 90 MHz ^1H nmr spectrum of MHB was investigated. First of all, the spectrum of racemic MHB (30μℓ, 4.1×10^{-4}mol) in deuterochloroform (300μℓ) was obtained. $Eu(hfc)_3$ (0.04g, 3.3×10^{-5}mol) was then added to this solution of MHB and a second ^1H nmr spectrum obtained. The two spectra, together with the assignments for the individual signals, are shown in Figures 4.5.1.2(i) and (ii) respectively. It was seen that the presence of the shift reagent had caused the proton resonance signals

Figure 4.5.1.2 Effect of Chiral Shift Reagent $Eu(hfc)_3$ on ^1H nmr Spectrum of MHB







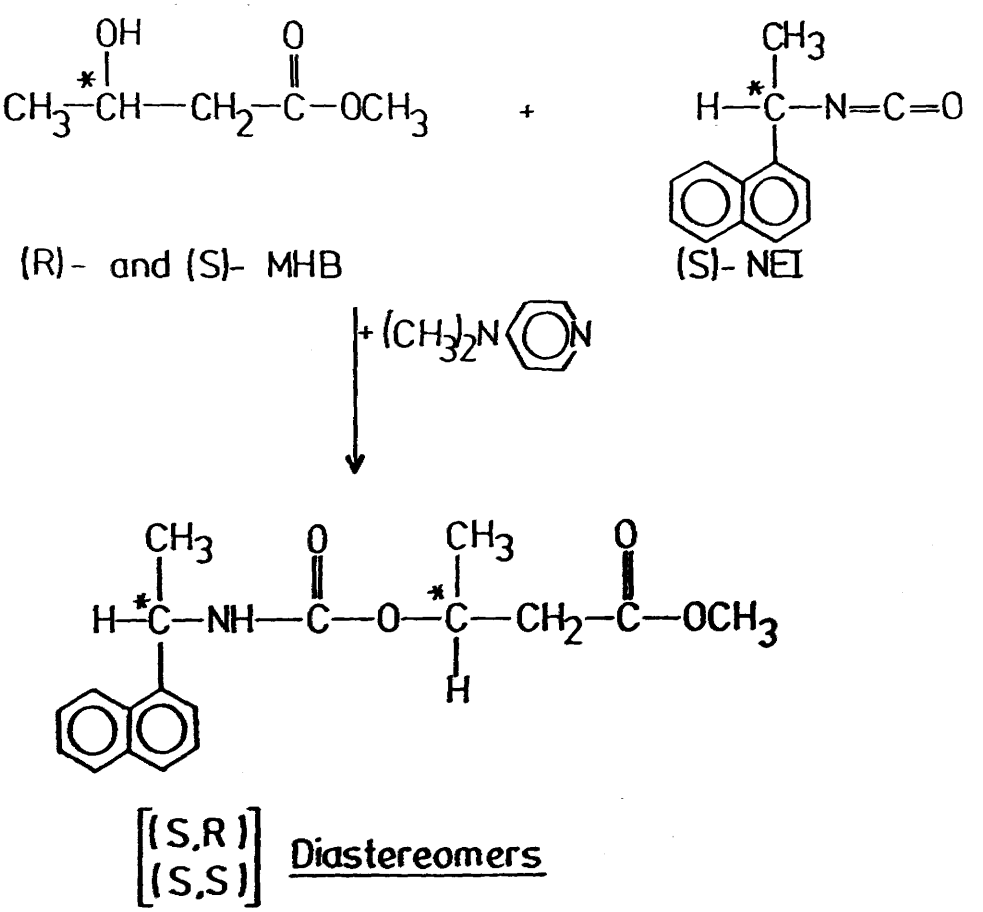
to undergo downfield shifts of different magnitudes; in fact the $-CH_2$ and $-OCH_3$ signals had coalesced to some extent. The most important feature was evident from the behaviour of the $-CH_3$ resonance signal; the doublet in (i) was transformed into two doublets in (ii). Thus, the signals corresponding to different enantiomers of MHB had become partially resolved. This same effect could be seen in the signal for the -C-H proton; unfortunately, however, all enantiomeric resolution was lost as a result of the pronounced line broadening which was also occurring. If the ^1H nmr spectra were to be obtained at, for example, 200 MHz instead of 90 MHz, it is possible that the two $-CH_3$ signals could be sufficiently resolved to allow the enantiomeric composition of MHB to be calculated from the relative peak areas. However, there remains the fact that any results obtained from nmr spectroscopic data are accurate only if very pure samples have been used.

4.5.2 Gas Chromatography

The technique of derivatising MHB with some chiral agent has already been described in Section 4.2.1. Success in separating diastereomers of MHB has recently been achieved using (S)-(+)-1-(1-naphthyl)ethylisocyanate, NEI, as the derivatising agent.[140] The reaction scheme is shown in Figure 4.5.2.1.

MHB (16 µℓ, 1.4×10^{-4} (R)- + 4 µℓ, 3.6×10^{-5} mol (S)-MHB) was heated overnight with NEI (40 µℓ) and a 5%

Figure 4.5.2.1 Reaction of MHB with (S)-(+)-(1-Naphthyl) Ethylisocyanate, NEI



solution of 4-dimethylaminopyridine in dichloromethane (40 µℓ) at a temperature of 60°C. The resulting solid was dissolved in dichloromethane (5ml) while any remaining, unreacted isocyanate was destroyed by the addition of methanol (1ml).

Gas chromatography of the diastereomers was carried out using a 25m long, 0.25mm i.d. stainless steel capillary column coated with dimethylpolysiloxane of film thickness 0.25 µm. The resulting chromatogram is shown in Figure 4.5.2.2.

Despite the fact that a reasonably satisfactory resolution of diastereomers was obtained, there was some evidence that thermal degradation had occurred to a slight extent. A possible solution to this problem may be found in altering the injection procedure, although no such attempts have yet been made.

4.5.3. High Performance Liquid Chromatography.

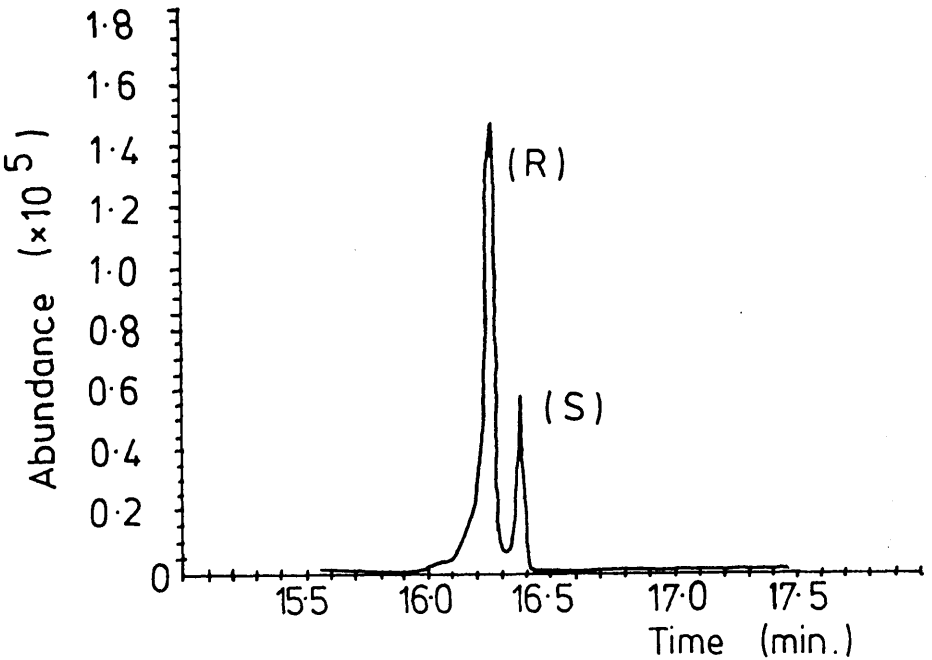
Investigations into liquid chromatographic techniques for the purpose of resolving the (R)- and (S)-enantiomers of MHB have only recently began. However, a partial separation of diastereomers of MHB, produced by some derivatisation process, has been achieved using a Particil 5 silica column,[140] a fact which indicates that this procedure may indeed be suitable as a basis for a method of analysis.

Figure 4.5.2.2 Gas Chromatogram of Diastereomers of (R)- and (S)-MHB with (S)-NEI

Carrier Gas (He) Flowrate = 2ml/min.

Column Temperature Profile :- Initial Temp. = 80°C (0 min.)
Ramp Rate = 12°C/min.
Final Temp = 275°C (8 min.)

Detection :- Selected ion - 214 a.m.u.



4.5.4 Closing Remarks.

The difficulties which have been described in this section as well as in Section 4.2 and 4.3 are perhaps directly reflected in the fact that, to date, all reports on the subject of the asymmetric hydrogenation of MAA wnich have been published have used polarimetry as the means whereby chiral recognition is effected. In fact, only once has an alternative technique been used in the field of heterogeneously catalysed asymmetric C=O hydrogenation reactions; in their investigations of the hydrogenation of β-keto sulphones with asymmetrically modified Raney nickel catalysts, Tai and co-workers used a chiral shift reagent in conjunction with ^{1}H nmr spectroscopy.[141] Perhaps it will be possible to replace polarimetry with a more accurate technique in studies of asymmetric hydrogenation reactions in the very near future, since efforts directed towards this achievement are at present being continued.

CHAPTER FIVE

TREATMENT OF RESULTS

5.1 Analysis of Reaction Mixtures using Gas Chromatography

As detailed in Section 3.5, quantitative analysis of hydrogenation reaction mixtures was carried out using gas chromatography.

5.1.1 Response Factors

In order to calculate the relative amounts of MAA and MHB present in any sample of a reaction mixture from its chromatogram, the response factor, R, of each had to be determined. For a substance x, R_x can be defined as the number of moles of x per unit area of chromatogram peak produced by pure x. Therefore, separate chromatograms of a 1 µl sample of pure MAA and MHB were obtained, and the area of the resulting peaks measured using a planimeter; the values for these areas were thus given in arbitrary units. By measuring the area of each peak produced over a series of ten 1 µl injections of MAA the error involved in performing gas chromatographic analysis was found to be ± 1%.

Values for R_x were calculated in the following way:-

$$R_x = \frac{\text{Peak Area of x}}{\text{No. moles of x in 1µl}} \qquad (5.1.1)$$

The units of R_x were, therefore, (area mol^{-1})

In theory response factors should be invariant from day to day, within the error of ± 1%. In practice, however the sensitivity of the detector varied slightly from one day

to another and so the response factors of MAA and MHB were determined before each experiment.

Typical retention times and response factors are shown in Table 5.1.1.

Table 5.1.1.

	MAA	MHB
Retention time (min)	60	77
Response factor (area mol^{-1})	1.78×10^{-5}	9.24×10^{-6}

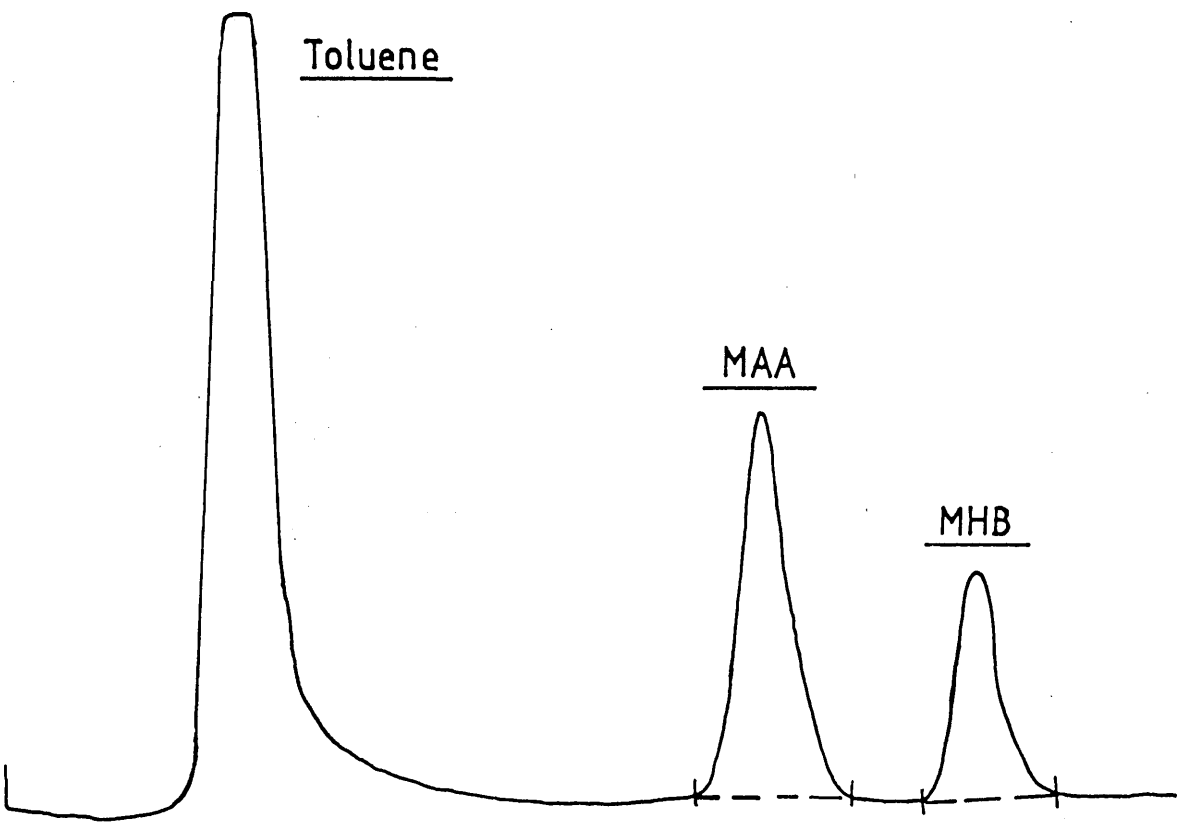
5.1.2 Calculation of Percentage Conversion of MAA

Knowing the response factor of each of MAA and MHB, the relative amounts of the two species present in a chromatogram, such as Figure 5.1.2, were then calculated and are shown in Table 5.1.2.

Table 5.1.2.

Compound	Response Factor (area mol^{-1})	Peak Area (arbitrary units)	No. moles present, n
MAA	1.72×10^{-5}	0.39	6.70×10^{-6}
MHB	1.11×10^{-5}	0.19	2.10×10^{-6}

Figure 5.1.2 Gas Chromatogram of Reaction Mixture, after Hydrogenation of MAA in Toluene with Raney Nickel Catalyst



The percentage conversion, P, of MAA to MHB was

$$P = \frac{\text{no moles MAA hydrogenated to MHB}}{\text{original no. moles MAA present}} \times 100\% \qquad (5.1.2.1)$$

Since

$$1 \text{ mole MAA} \xrightarrow{H_2} 1 \text{ mole MHB}$$

it followed that the numerator in equation 5.1.2.1 was equal to the number of moles of MHB present in the reaction mixture, after the hydrogenation reaction had been carried out.

Simplification of the denominator was also possible. It was concluded that all the MAA originally present either remained in the reaction mixture or was hydrogenated to MHB, since the catalyst was found to be 100% product selective. The basis for this conclusion is discussed in Section 6.1.

Thus the expression for P became

$$P = \frac{n_{MHB}}{n_{MAA} + n_{MHB}} \times 100\% \qquad (5.1.2.2)$$

where the values for n_{MAA} and n_{MHB} were as shown in Table 5.1.2.

For the reaction mixture which produced Figure 5.1.2 on chromatographic analysis, P was calculated from equation 5.1.2.2 to be 24%.

5.2 Calculation of Enantiomeric Excess from Polarimetric Measurements.

Suppose a solution of a chiral compound is of concentration c $mg(ml^{-1})$ and

c_R = concentration of (R)-enantiomer

c_S = concentration of (S)-enantiomer

then $c = c_R + c_S$ (5.2.1.)

The optical rotation, α, which results from passing linearily polarised light through this solution will be non-zero, and therefore measurable, provided there is an excess of one enantiomer over the other; if the (R)-enantiomer is in excess, then

$$c_R' = c_R - c_S \qquad (5.2.2.)$$

where c_R' is the excess concentration of (R). The existence of c_R' will produce the optical rotation, α, observed according to the equation

$$[\alpha]_\lambda^T = \frac{\alpha}{c_R'} \qquad (5.2.3.)$$

where the parameters are as described in Section 4.

In enantioselective hydrogenation, it is conventional to quote results in terms of "enantiomeric excess", where

$$\text{enantiomeric excess, e.e} = \frac{c_R - c_S}{c_R + c_S} \times 100\%$$

$$= \frac{c_R'}{c} \times 100\% \qquad (5.2.4.)$$

Using equation 5.2.3, c_R' can be calculated from polarimetric measurements, provided $[\alpha]_\lambda^T$ for the material in the appropriate solvent is known. The value of the total concentration c, of the chiral compound will depend on how much of the prochiral substrate has been hydrogenated during the reaction; c can be calculated if the percentage conversion, P, of substrate to product is known from gas chromatography, as detailed in Section 5.1. An example of the calculation of enantiomeric excess from both gas chromatographic analysis (shown in Figure 5.1.2.) and polarimetric measurements for a typical reaction mixture is shown in Table 5.2

Table 5.2

[a]P (%)	c_{MHB} (mgml^{-1}) in reaction mixture	α	[b] $[\alpha]_{589}$ nm	c_R' (mgml^{-1}) from 5.2.3	e.e. (%) from 5.2.4
24	26.3	-0.064°	-21.1°	3.0	-11

a:- value of percentage conversion to MHB of 3g MAA in 25ml toluene.

b:- Specific rotation of pure (R)-MHB in toluene

Since (R)-MHB is laevorotatory, it is conventional to denote an excess of this enantiomer by a negative value for the enantiomeric excess; it then follows that a positive value for the enantiomeric excess is indicative of an excess of dextrorotatory (S)-MHB. The value obtained for the enantiomeric excess of MHB in Table 5.2 was, however, subject

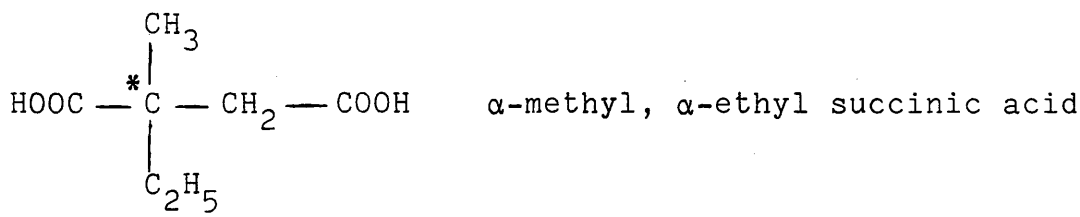
to a further correction, as discussed in Section 5.3.

5.3 Enantiomeric Recognition and Interactions.

Regardless of whatever physical technique is used as a means of chiral recognition, an important factor must be taken into consideration for the technique to provide accurate determinations of enantiomer ratios.

In 1969 Horeau[142] found that, for solutions of predetermined enantiomeric composition of α-methyl, α-ethyl succinic acid, shown in Figure 5.3.1, in chloroform, the optical purity, measured using polarimetry, differed from the actual values.

Figure 5.3.1.



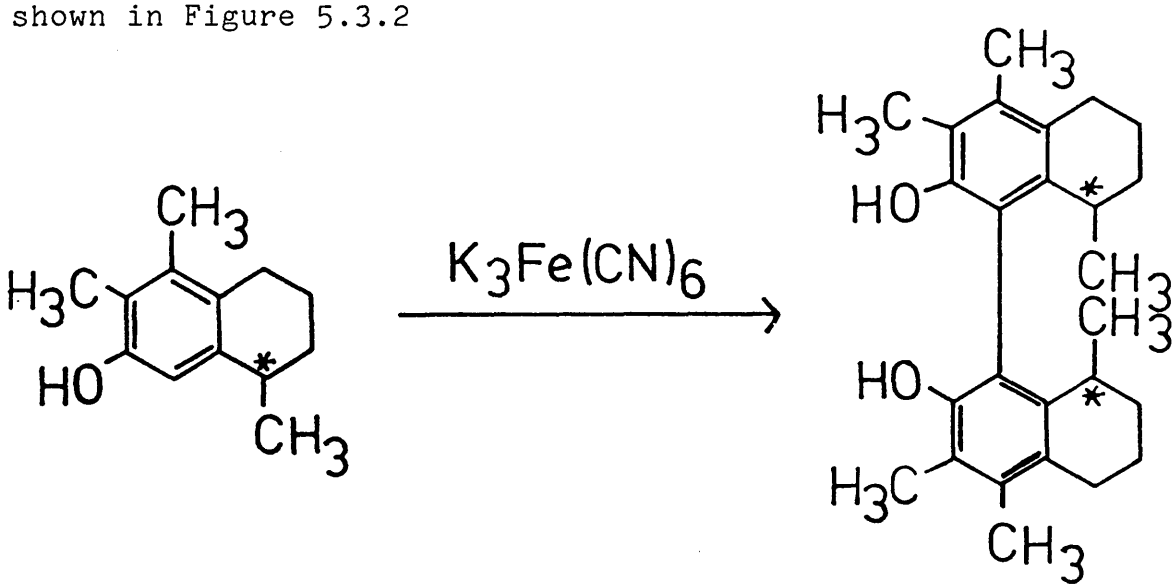
α-methyl, α-ethyl succinic acid

Agreement of the two sets of values for optical purity was particularly poor at low enantiomeric excesses, while, at higher excesses, ideal correlation was obtained. Horeau attributed this finding to the effect of the different enantiomeric interactions possible at the two extremes, which are described in Table 5.3.1.

Table 5.3.1

Enantiomeric Composition of solution	Low excess of (R)	High excess of (R)
Possible interactions	(R)-(R) (R)-(S) both present	Mainly (R)-(R) present

The additional presence of (R)-(S) to (R)-(R) interactions at low excesses is of such a nature that the measured optical purity is affected. This phenomenon was later discovered to affect the path of the chemical reaction of some optically active substances, for example the dimerisation of (S)-7-hydroxy-1,5,6-trimethyl-1,2,3,4-tetrahydronaphthalene,[143] shown in Figure 5.3.2



(S)-I (S,S)-II

Figure 5.3.2

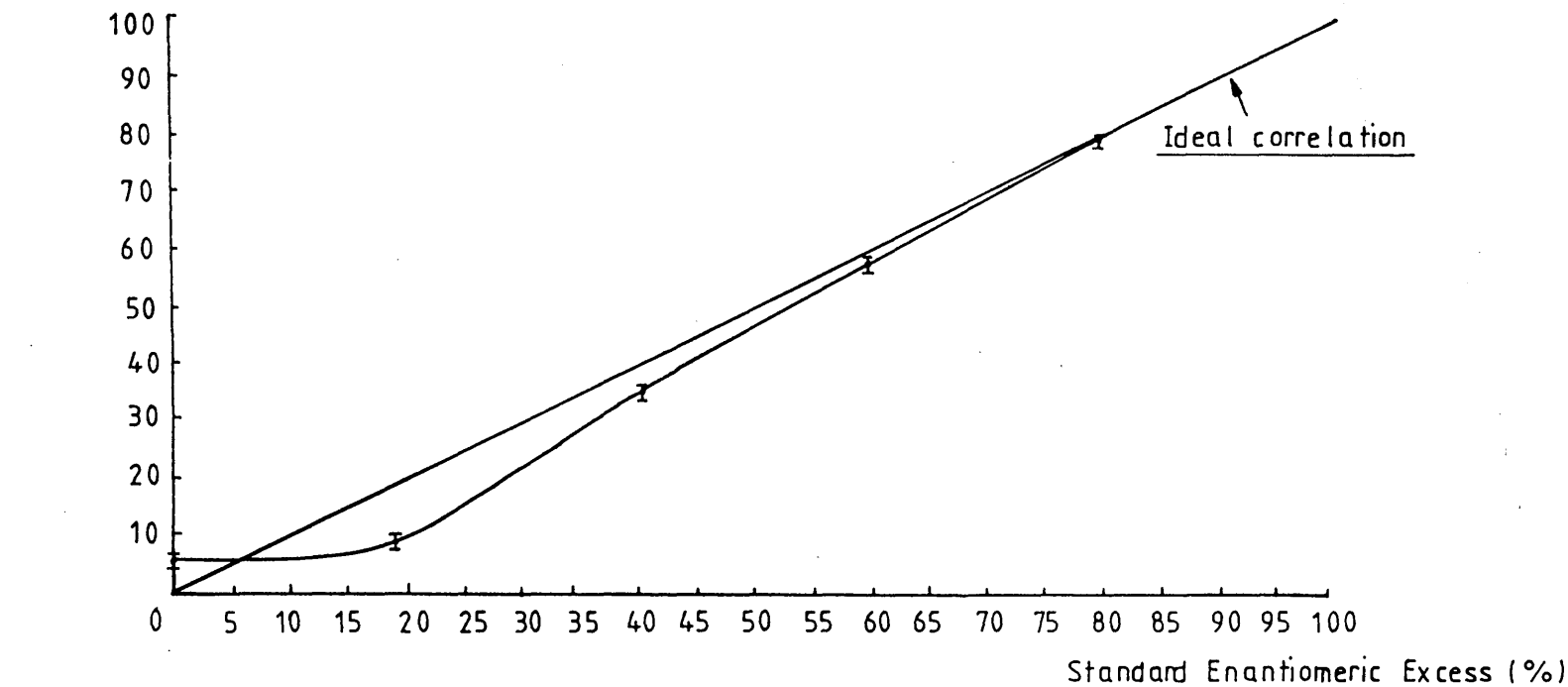
Two forms of the dimer II are possible - (S,S)-trans and (S,S)-cis. It was found that different dimer products were formed depending on whether pure (S)-I or racemic I was used as the starting material. Since all

other factors remained unchanged, this phenomenon must be due to the influence of the (R)-enantiomer on the nature of reaction between two (S)-enantiomers, by means of non-bonded interactions. Since MAA, the species which was being hydrogenated in this work, is achiral, this effect does not arise during the hydrogenation reaction itself and so only the effect of enantiomeric interactions in the determination of the enantiomeric composition of MHB need be considered.

It was therefore necessary to carry out a careful calibration of measured versus actual values of optical purity of MHB in appropriate solvents. In fact, it was found that the effect showed little variation between solvents such as toluene, methyl propionate and butanol (that is, solvents used for reactions) and a typical relationship is shown in Figure 5.3.3. This correlation was obtained from polarimetric measurements of α values produced by solutions of predetermined enantiomeric composition. The total concentration, c, of these solutions was around 20 $mgml^{-1}$ in each case in an attempt to keep solvent interactions constant. Enantiomeric excess was calculated as previously explained in Section 5.2 using equations 5.2.3 and 5.2.4. Therefore, after using polarimetry to calculate the enantiomeric excess of MHB contained in solution following hydrogenation of MAA, this calibration curve must be used as a means of correction for the effect of enantiomeric interactions on readings obtained. This is of particular importance for values of enantiomeric

Figure 5.3.3

Calibration of standard v measured Enantiomeric Excess (%)



excess calculated to be 50%, where deviation from the true values was of a substantial amount.

For the example in Section 5.2, the enantiomeric excess was calculated to be -11%, from polarimetric measurements. Using the method of correction explained in this section, this value is increased to -19%.

The error in values of enantiomeric excess measured by polarimetry was calculated to be ±2%; the error in the corresponding actual enantiomeric excesses, determined using Figure 5.3.3, was, however, dependent on the magnitude of the measured excess.

CHAPTER 6

RESULTS AND DISCUSSION

6.1 Effect of Raney Nickel Catalyst on the Reaction $MAA \xrightarrow{H_2} MHB$

Figure 6.1.1 shows the gas chromatograms of both pure MAA and of MAA in butanol, that is, before any hydrogenation had been attempted. The retention times are shown in Table 6.1.1.

Table 6.1.1

Chromatogram	Retention Time of MAA (min.)
(i) pure MAA	60
(ii) MAA in butanol	61

Initially, all hydrogenation reactions were carried out as described in Section 3.3.2. The gas chromatogram of the reaction mixture, following treatment of MAA with hydrogen in the absence of any catalyst, is shown in Figure 6.1.2. It is clear that little or no change had occurred in the chemical composition of the reaction mixture, as shown in Table 6.1.2.

Table 6.1.2.

Gas Chromatogram	MAA Peak Area
6.1.1 (ii) - peak no. II	0.52
6.1.2 - peak no. II	0.51

Figure 6.1.1 Gas Chromatograms of (i) — — — pure MAA

(ii) ——— pure MAA in butanol

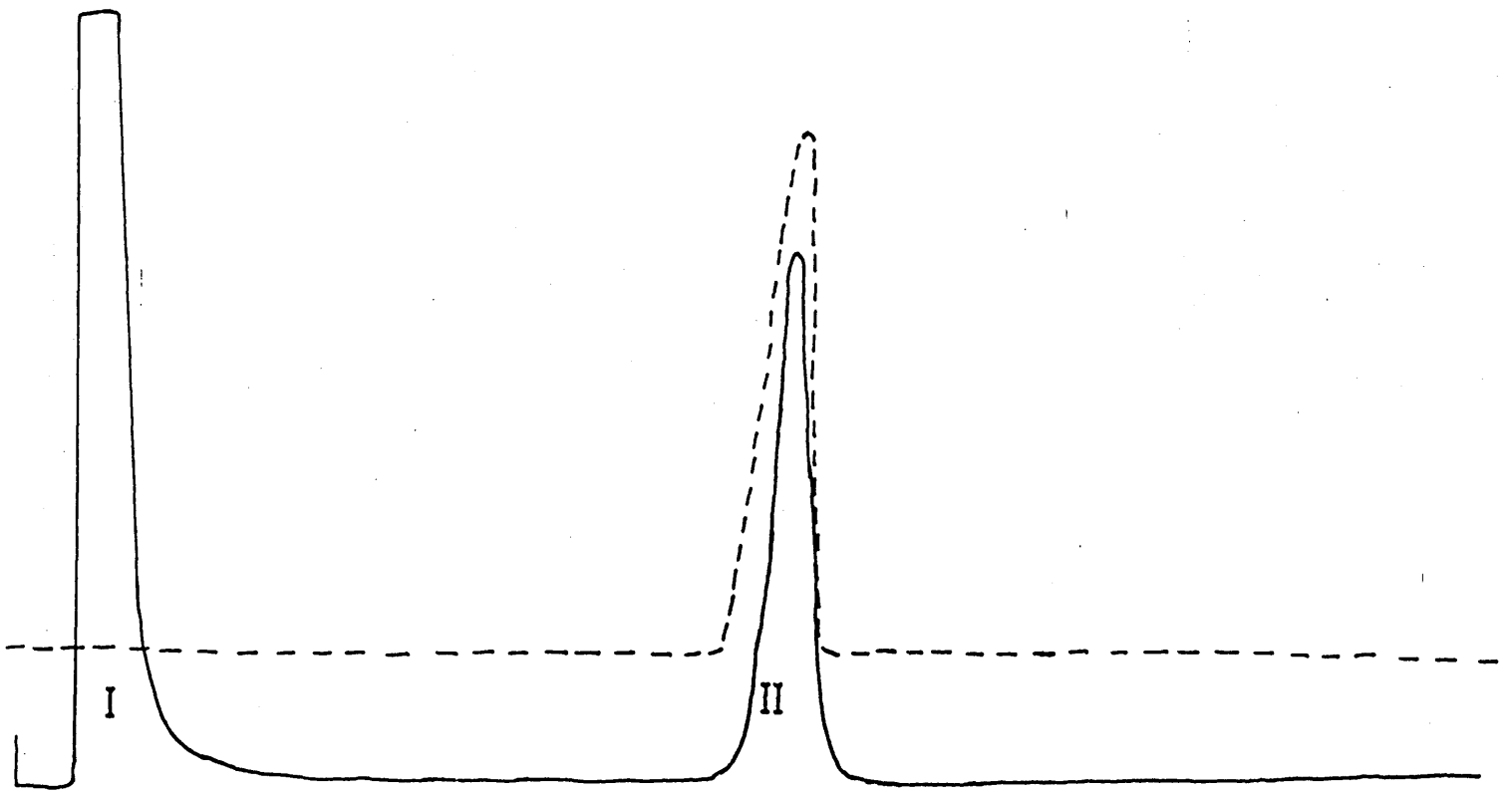
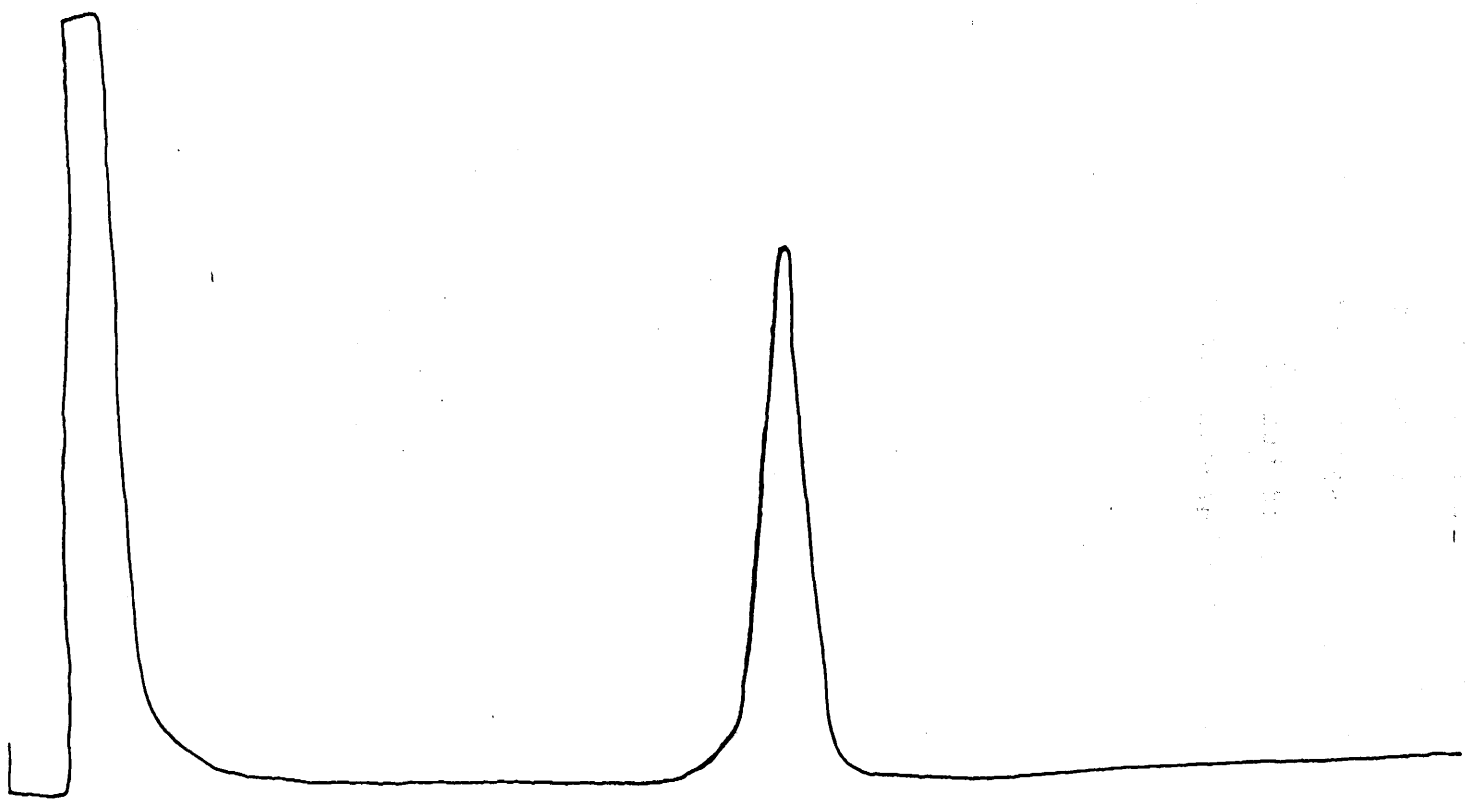


Figure 6.1.2 Gas Chromatogram of Reaction Mixture in Butanol after hydrogenation of MAA in the absence of catalyst



The two peak areas of MAA are within 2% of each other - the discrepancy is therefore within the accepted error of ±1% which was found by calculation, as described in Section 5.1.1. Figure 6.1.3(i) shows the effect of the presence of Raney nickel catalyst, prepared as described in Section 3.2.1, in the hydrogenation reaction. The presence of a third component in the product mixture, in addition to that of butanol and MAA, is evident from the appearance of peak III, the retention time of which corresponds to that of MHB:-

Table 6.1.3

Gas Chromatogram	Retention Time (min.)
6.1.3 (i) - peak no. III	78
6.1.3 (ii)	77

Consequently, peak III in chromatogram 6.1.3(i) is interpreted as MHB, produced during the Raney nickel-catalysed hydrogenation of MAA. Since chromatogram 6.1.3(i) contains only peaks due to solvent(I), MAA(II) and MHB(III) respectively, it is concluded that the catalyst was 100% product selective, that is, there were no reaction products other than MHB. This MHB, however, was found to be optically inactive and so a racemic mixture of chiral product had been obtained using an unmodified Raney nickel catalyst.

Figure 6.1.4 shows the effect of increasing the amount of Raney nickel in the hydrogenation reaction mixture on the

Figure 6.1.3 Gas Chromatograms of (i) ——— reaction mixture in in butanol, after hydrogenation of MAA with Raney nickel catalyst (ii) – – – – pure MHB

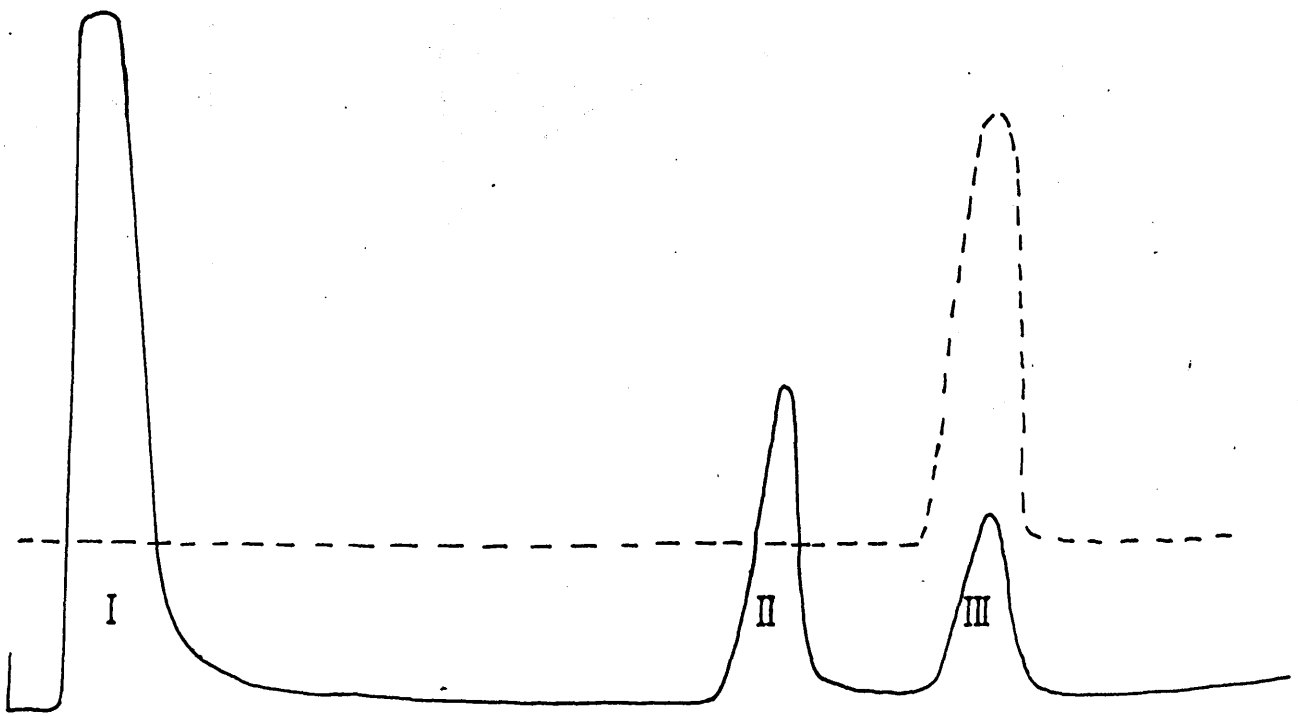
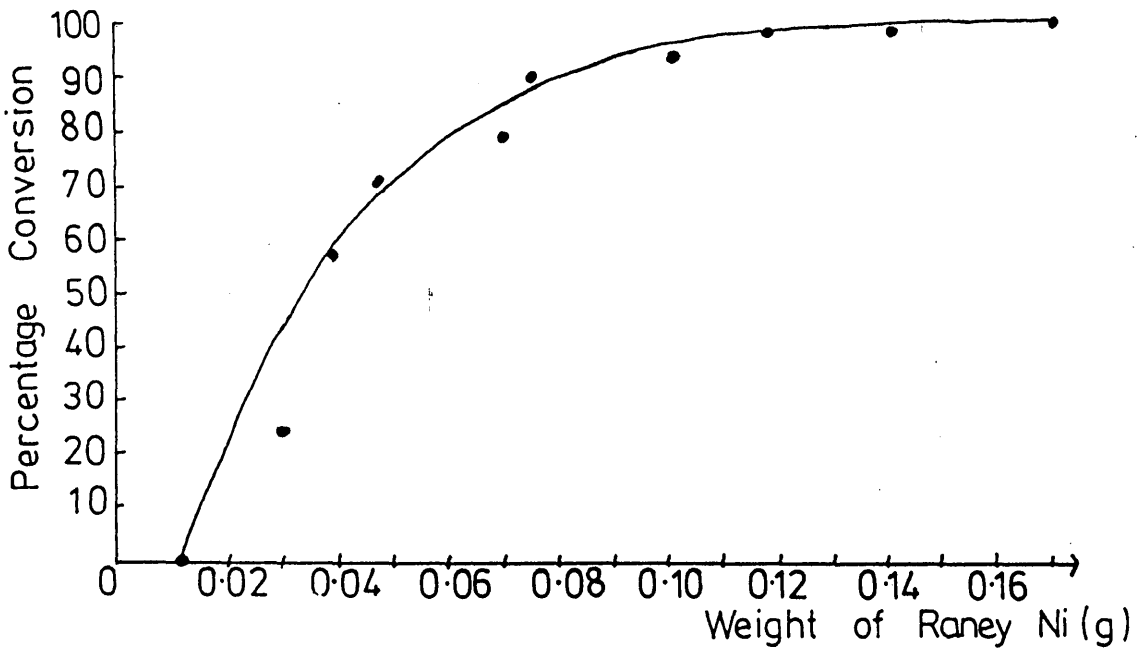


Figure 6.1.4 Weight of catalyst v Percentage Conversion for

$$MAA \xrightarrow[H]{RNi} MHB$$

(2g MAA in 20ml butanol)



percentage conversion of MAA. Having established that Raney nickel is essential for hydrogenation to occur, the effect of using the same catalyst in second and subsequent hydrogenation reactions was investigated; the results are shown in Table 6.1.4.

Table 6.1.4

Reaction Number	Conversion (%)
1	65
2	16
3	0

(2.5g MAA/0.069g Raney Ni in 20ml butanol)

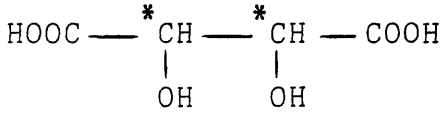
It is seen from Table 6.1.4 that the hydrogenating activity decreased by a large amount when the catalyst was used more than once and, in fact, totally disappeared after using the same catalyst in three successive reactions. This rapid loss of activity was perhaps due to sintering of metal particles during the reaction itself, which was carried out at a temperature of 70°C. A second factor may have been a consequence of the process of filtering the catalyst from reaction mixtures; despite careful precautions to prevent the pyrophoric catalyst from becoming completely dry, some oxidation of nickel metal could have occurred. Regardless of the validity of these two possible explanations, however, the results showed that it was necessary to use a

fresh sample of catalyst in each experiment.

The fact that a racemic mixture of MHB had been obtained using an unmodified catalyst had shown that Raney nickel itself did not possess any enantio-differentiating ability. The next step was, therefore, to investigate the effect of modifying the metal catalyst with some optically active agent.

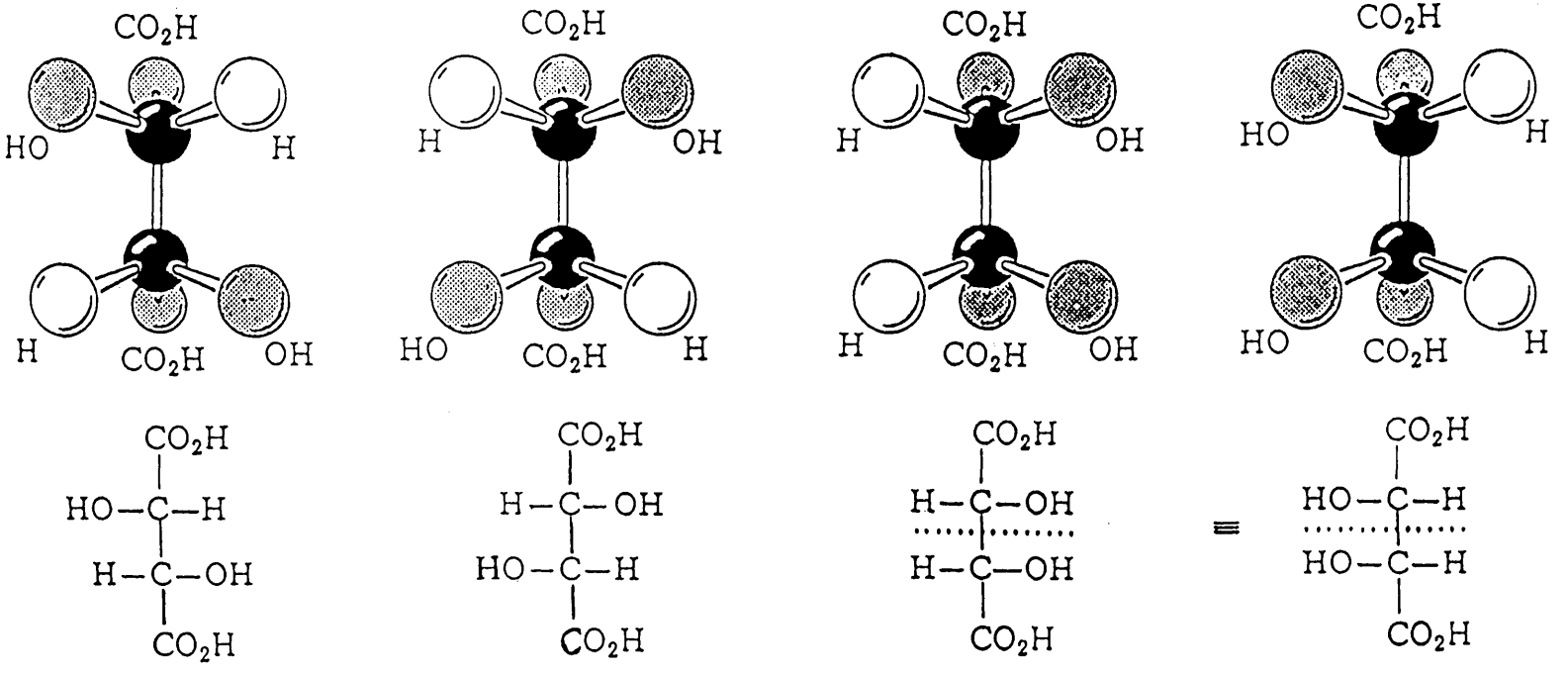
6.2 Tartaric Acid - Modified Raney Nickel

Izumi's finding that the α-hydroxy acid, tartaric acid,



was extremely effective as an asymmetric catalyst modifier has already been described in Section 1.7.1.[55] Since the molecule contains two, identical chiral centres, there are three possible stereoisomeric configurations which can be adopted and these are shown in Figure 6.2.1. The two optically active forms, (S,S)-(-)- and (R,R)-(+)-, are enantiomeric while the optically inactive meso form consists of the two, equivalent (S,R)- and (R,S)- configurations. Naturally occurring tartaric acid has the (R,R)-(+)- configuration and, therefore, in the majority of experiments which were to be carried out with an asymmetrically modified Raney nickel catalyst, the relatively inexpensive (R,R)-(+)- enantiomer of tartaric acid was used as the optically active agent.

Figure 6.2.1 The Tartaric Acids



(S,S)-(-)- (R,R)-(+)- [(R,S) and (S,R)] = MESO

The conditions for the digestion of Raney alloy and modification of Raney nickel, which were given in one of Izumi's reports were followed exactly in initial investigations and the details of these two procedures are given in Sections 3.2.1 and 3.2.2 respectively; in Section 3.2.2, the pH of the modifying solution was adjusted to the value of 5.1.

As discussed in Chapter 4, polarimetry was used as the means of determining the enantiomeric excesses of MHB produced during reactions; furthermore, the fact that the optical rotation of MHB was measured while it remained in the reaction mixture was explained in Section 3.6. However, there were two potentially significant sources of error involved in this technique:-

(i) The possibility of the enantiomeric form of MHB changing in the reaction solution as a result of it remaining in contact with the catalyst before filtration.

(ii) Dissolution of the dextrorotatory tartaric acid modifier from the Raney nickel catalyst into the reaction mixture.

It was essential, therefore, to investigate whether either of these processes was occurring under the reaction conditions employed. First, MAA (2.5g) and racemic MHB (0.5g) were dissolved in either butanol or toluene (25ml) and the optical rotation, α_1, produced by the resulting solution measured. Together with modified Raney nickel catalyst (0.9g), this solution was added to the reaction vessel which is shown in Figure 3.3.2. Thus, the species contained in the vessel were

representative of a typical reaction mixture during a liquid phase hydrogenation of MAA under atmospheric pressure of hydrogen, with one exception; no hydrogen was at any time added to the system. Using conditions which were therefore similar to those for hydrogenation, described in Section 3.3.2, this mixture was shaken overnight at 70°C. Following this treatment, the "reaction mixture" was filtered, and the optical rotation, α_2, again measured. Thus, any change in the optical rotation of the solution containing MAA and MHB as a result of it being heated overnight, in the presence of modified Raney nickel, would be observed. The results obtained using butanol and toluene as solvents are shown in Table 6.2.1.

Table 6.2.1.

Solvent	α_1	α_2
Butanol	+ 0.001	- 0.001
Toluene	- 0.002	+ 0.001

(C_{MHB} = 18.0mgml^{-1} in the "reaction mixture")

It is clear from Table 6.2.1 that in neither case did the optical rotation alter by any significant amount. In view of this, there is no evidence to suggest that either a change in configuration of MHB or dissolution of tartaric acid was occurring. This latter fact is not surprising when the solubility of the modifier in a variety of solvents is considered (R,R)-tartaric acid is known to be extremely soluble in water, insoluble in aromatic solvents such as benzene and toluene and only moderately soluble in higher alcohols such as butanol.[144]

Since dissolution of tartaric acid from the modified catalyst into a surrounding aqueous medium would be expected, water was not thought to be a suitable solvent for the liquid phase hydrogenation of MAA.

The conclusion from this investigation is that valid results were obtained by measuring the optical rotation produced by MHB while it remained in the reaction mixture.

6.3 The Effect of Tartaric Acid-Modified Raney Nickel on MAA $\xrightarrow{H_2}$ MHB.

The effect of the modification process on the activity and enantio-differentiating ability of a Raney nickel catalyst was investigated; modification with (R,R)-tartaric acid was carried out as described in Section 3.2.2 at a pH of 5.1. The results which were obtained are shown in Table 6.3.1.

Table 6.3.1.

Catalyst	Conversion (%)	Enantiomeric Excess (%)
Raney Ni	90	0
*MRNi	36	0

(3.0g MAA/0.15g catalyst in 25ml butanol)

The decrease in catalyst activity which had occurred was reflected in the much lower conversion of MAA obtained using the modified as opposed to the unmodified catalyst. This is consistent with the idea that tartaric acid molecules were

being adsorbed on to the nickel surface, thereby causing a simultaneous reduction in the total number of active sites available for MAA hydrogenation. Despite this loss of hydrogenation activity, there was a complete lack of any accompanying appearance of enantioselectivity. This finding is in sharp contrast to the claims contained in Izumi's report that an enantioselective Raney nickel catalyst was produced by the process of modification which is described in Section 3.2.2. The initial choice of butanol as a solvent for the reaction had been made largely because of its conveniently high boiling point of 117°C, which enabled reactions to be carried out at a temperature of 70°C. The effect of using different solvents was then investigated, in an attempt to obtain a non-zero enantiomeric excess and the corresponding results are shown in Table 6.3.2.

Table 6.3.2.

Solvent	Conversion (%)	Enantiomeric Excess (%)
Butanol	32	0
Toluene	27	0
Methyl propionate	19	0
Ethyl acetate	14	0
Methyl acetoacetate	4	0
Dimethyl formamide	0	-

(3.0g MAA/0.15g *MRNi in 25ml solvent)

These results show that the choice of solvent did in fact have a considerable influence on the conversion; it

is interesting to compare the extents of conversion with the dielectric constants of the solvents[144], the values of which are shown in Table 6.3.3.

Table 6.3.3.

Solvent	Dielectric Constant, ε
Butanol	17.8
Toluene	2.4
Methyl Propionate	5.5
Ethyl acetate	6.0
Methyl acetoacetate	15.0 (approx)
Dimethyl formamide	109 (approx)

Although there is no strict correlation between conversion and solvent dielectric constant, it is apparent that the use of a solvent with a very high value of ε, that is, dimethyl formamide, resulted in a total lack of hydrogenation. This latter finding is in some way consistent with Klabunovskii's observation that log (optical yield) varied inversely with the magnitude of the dielectric constant of the solvent.[76]

A second point of interest is the detrimental effect of using MAA itself as the reaction solvent. It was noticed that the MAA became progressively more green in colour as it was heated in the presence of the catalyst and so the inference was that a certain amount of catalyst corrosion was taking place; this observation is in agreement with one made earlier by Harada.[77]

Despite the fact that the solvent had been found to exert a strong influence on the extent of reaction of MAA, the investigations had failed to lead to the observation of any enantioselectivity. Nonetheless, the results proved to be extremely useful, in that either toluene or butanol should be used as the reaction solvent if maximum conversion of MAA were to be obtained.

The last point of interest which arose during this series of experiments involved the extent to which toluene was purified before use. Undoubtedly, the desulphurisation process described in Section 3.1 was essential, since the presence of any sulphur-containing compounds would result in the immediate poisoning of a Raney nickel catalyst. There was also the question of whether it was advisable to dry the toluene thoroughly with sodium wire; the results obtained from varying the pretreatment of toluene are shown in Table 6.3.4.

Table 6.3.4.

Solvent	Conversion (%)	Enantiomeric Excess (%)
25.0ml dry toluene	0	-
24.5ml dry toluene + 0.5ml water	4	0
23.0ml dry toluene + 2.0ml water	4	0
25.0ml toluene not dried after desulphurisation	30	0

(3.0g MAA/0.45g *MRNi)

It is clear from Table 6.3.4 that considerable

amounts of water are required to be present if any hydrogenation is to occur at all. The phenomenon of an increase in reaction rate during the liquid phase hydrogenation of MAA as a result of the presence of small amounts of water has been observed with two, quite different catalytic systems, by Ninomiya and Solodar respectively. The first was a heterogeneous Raney nickel catalyst,[145] modified with either an amino or a hydroxy acid, while the second was a homogeneous rhodium-diphosphine complex catalyst.[146] In addition, the water level in the reaction mixture was found to assume a critical role in determining the optical yield of the reaction; Ninomiya and Solodar both observed that the optical yield tended to decrease as the water content increased. No comment could be made as to the influence of water on the enantioselectivity of the reaction in toluene with a tartaric acid-modified Raney nickel catalyst, since the value of the enantiomeric excess in Table 6.3.4 remains at zero, in spite of variations in the water content of the solvent. However, the fact that small amounts of water were required for the reduction of MAA is consistent with the observations that water produced an increase in reaction rate, although neither Ninomiya nor Solodar reported that there was a total lack of hydrogenation in the absence of any water.

Two questions in particular are raised from these observations.

(1) First, the exact function of the water molecules must be

considered. Any increase in the rate of a heterogeneously catalysed liquid phase hydrogenation reaction could arise from an influence on any one of the following steps:-

(i) Diffusion of substrate or hydrogen through the solvent.

(ii) Adsorption of substrate or hydrogen on to the catalyst surface.

(iii) Hydrogenation

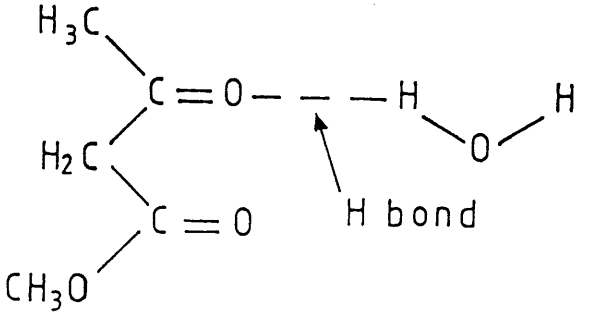
(iv) Product desorption.

In addition, it must be remembered that, in the case of an asymmetrically modified catalyst, a further effect of water could be to alter the amount of modifier adsorbed on the catalyst surface; that is,tartaric acid, for example, could re-dissolve in the water, whereas its poor solubility in solvents such as toluene would prevent this dissolution from occurring in the absence of water. If tartaric acid were indeed desorbed from the catalyst surface, it could mean that more active sites were re-generated for the purpose of MAA hydrogenation. In this situation it would be expected that the removal of tartaric acid from the catalyst would result in a decreased optical yield and so this provides an alternative explanation for the observations made by Ninomiya, who made no attempt to correlate the two effects of increased rate and decreased optical yield. In an effort to determine whether or not tartaric acid was being removed from the catalyst surface, a separate experiment was carried out, in which a solution of MAA in wet toluene was shaken overnight at 70°C with a sample of tartaric acid-modified Raney nickel catalyst. However, there was no change in the optical rotation of the

solution as a result of this treatment. If any dextro-rotatory tartaric acid had in fact dissolved in the solution of MAA, it follows that a positive optical rotation would have been observed. Furthermore, hydrogenation of MAA in dry toluene did not occur when an unmodified Raney nickel catalyst was used, while some conversion was obtained in wet toluene. Thus, it is unlikely that the dissolution of tartaric acid was responsible for the results in Table 6.3.4. These results, however, were obtained using reaction conditions which differed slightly from those in Ninomiya's experiments - in particular, the relative amounts of water added to reaction mixtures were much larger in the latter set of experiments. In view of this, the possibility of dissolution of tartaric acid occurring in Ninomiya's investigations could not be ruled out.

Returning to the results shown in Table 6.3.4, it seems unlikely that trace amounts of water would greatly affect either the adsorption of hydrogen or MAA, or the desorption of MHB. Instead, it appears more likely that the interference of the water molecules was occurring during the hydrogenation step itself and that this interference was the same, regardless of whether or not an asymmetric modifier was present on the catalyst. It is possible that some kind of interaction was occurring between the water molecules and the adsorbed substrate, perhaps as a result of hydrogen bonding between the two polar species. If this is the case, then the

carbonyl group of MAA could be involved:-



The carbonyl C=O bond would thus be weakened; since it is this bond which is the site for hydrogenation, any bond weakening which occurred would lower the activation energy for the process of hydrogen insertion. If this step is rate determining, the overall rate of hydrogenation would be increased. This hypothesis could also be applied to Ninomiya's observations of an increase in the rate of hydrogenation and, furthermore, if the interaction between the water molecule and an adsorbed MAA species was stronger than that between adsorbed MAA and tartrate species, it is conceivable that the former interaction would occur at the expense of the latter. Consequently, the effect of the chiral template would be lost and so the optical yield would decrease. A similar hydrogen-bonded interaction would be possible between substrate and alcohol molecules and, certainly, it can be seen from Table 6.3.2 that the use of butanol as the reaction solvent resulted in the highest conversion of MAA obtained. However, there

have been no reports of a decrease in optical yield caused by the presence of alcohol molecules. Methanol itself has in fact been used in the atmospheric pressure hydrogenation of MAA in experiments carried out by Bostelaar and Sachtler[108,118] although neither the reason for their choice of solvent nor any optical yield obtained on using other solvents was given.

The third and final possible reason for the effect of water is that it in some way altered the ability of hydrogen gas to diffuse through the reaction solution so that it could reach the catalyst surface and subsequently become adsorbed. If this is true then the explanation would automatically extend to the results obtained on changing the reaction solvent, which are shown in Table 6.3.2.

(2) The second question which arises from these investigations concerns the similarity between the results reported for the heterogeneous and homogeneous reaction systems. This could, of course, have been entirely coincidental, but, nonetheless, the matter could not be ignored. Unfortunately, Solodar offered no explanation for his results using asymmetric homogeneous catalysts and so it was not possible to compare any suggested mechanisms with those which have been presented for heterogeneous catalysts. However, the main point which is prompted by the similarity in behaviour of the two types of catalyst concerns whether or not individually modified nickel atoms function in a manner very similar to that of homogeneous catalysts. It is certainly true that a nickel

metal surface as well as modified nickel atoms are necessary for a catalyst to be enantioselective, since using a nickel catalyst modified only with a nickel-tartrate complex resulted in the production of racemic MHB.[65] However, there is also the idea that the nickel-modifier complex is only loosely bound to the remainder of the bulk nickel metal and so can be considered almost as a single molecular entity and therefore as a "quasi-homogeneous" catalyst. This suggestion will be considered further in a subsequent section.

Quite apart from the validity of any of the suggested theories regarding the effect of water or the similarity in behaviour between the heterogeneous and homogeneous catalytic systems, the valuable information which was obtained from the results in Table 6.3.4 in relation to future experimental work was that, if it were to be used as the reaction solvent, toluene should first be desulphurised, but not dried.

The effect of varying the reaction solvent had initially been investigated in an attempt to observe enantioselectivity during the process of hydrogenation. Despite the fact that extremely interesting and useful results had been obtained, it had become obvious that the tartaric acid-modified Raney nickel catalyst did not possess any enantiodifferentiating ability. Consequently, it was necessary to carry out extensive series of investigations involving careful scrutiny of the various parameters in the modifying procedure.

6.4 Variations in the Procedure for Modification.

The Raney nickel catalyst used in all of the experiments which have been described was modified at a pH of 5.1 and so the outcome of varying the pH of the tartaric acid modifying solution was studied in some detail. The results are shown in Figure 6.4.1. It can be seen that the modifying pH had very little influence on the conversion of MAA until strongly alkaline conditions were attained; neither was there any change in the enantioselectivity, which maintained a value of zero throughout. In these experiments the catalyst had been freshly prepared from the starting material, Raney alloy, for immediate use and so at no stage had either modified or unmodified Raney nickel been stored under any solvent for a prolonged period of time. However, contrasting reports regarding the deterioration of catalytic activity of Raney nickel with increasing storage time have appeared in the literature; claims of increased storage time having little effect as well as a detrimental effect have been made.[147,148] In view of these claims, samples of unmodified Raney nickel were stored under methanol for a period of about two weeks and then the usual modification procedure carried out at a pH of 5.1. When these catalysts were used for reaction purposes, enantiomeric excesses of about -20% were obtained, although these results, which are shown in Table 6.4.1, were not always reproduced.

Figure 6.4.1

Percentage Conversion / Enantiomeric Excess v pH of Modifying Solution

for MAA $\xrightarrow[H_2]{MRNi}$ MHB

(3g MAA / 0·45g catalyst in 25ml toluene; reaction temp. = 70°C)

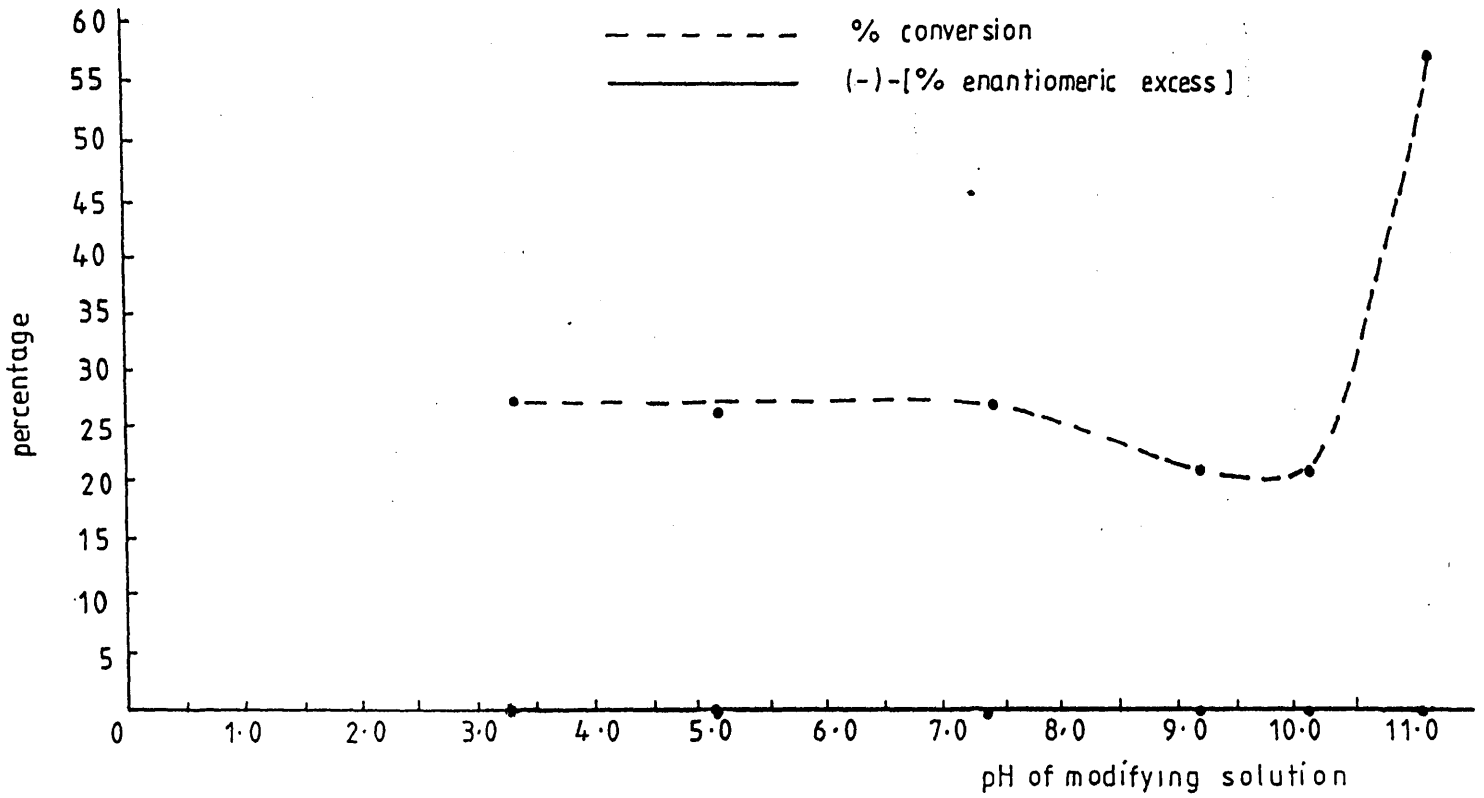


Table 6.4.1

Conversion (%)	-(Enantiomeric Excess) (%)
22	-19
20	-21
18	-22

(3.0g MAA/0.45g *MRNi in 25ml toluene)

Clearly the effect of catalyst storage on the conversion of MAA was small. However, zero values of enantiomeric excess were obtained with a greater frequency than non-zero values and so little comment can be made concerning the enantio-differentiating ability of the modified catalysts.

Two alterations were next made to the method of catalyst modification, in an effort to obtain reproducible enantioselectivity in hydrogenation reactions:-

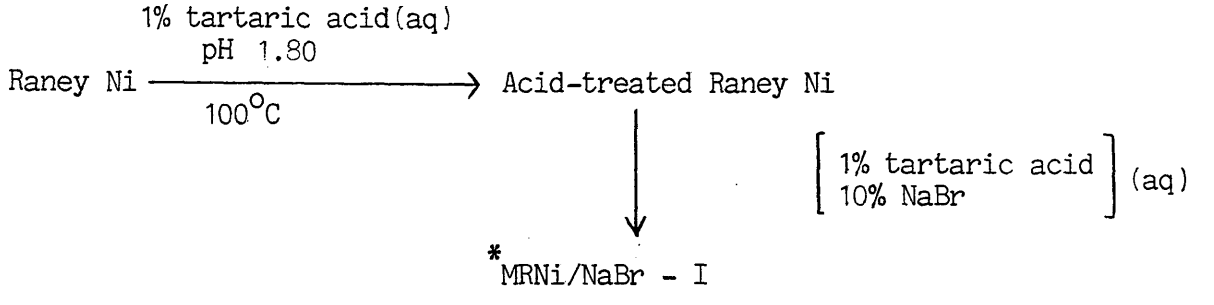
(i) Following reports that the inclusion of an alkali halide as a co-modifier with tartaric acid resulted in a catalyst with enhanced enantio-differentiating properties, sodium bromide was incorporated with tartaric acid into the modifying solution.

(ii) The temperature of modification was increased from 0 to 100°C.

Two alternative methods of catalyst preparation are described in Sections 3.2.3.I and II respectively. In the

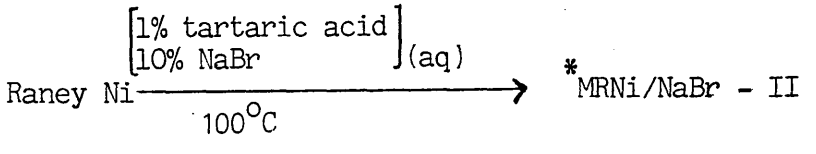
former, the catalyst was modified in two stages: treatment of Raney nickel at 100°C with tartaric acid was followed by modification with tartaric acid and sodium bromide at 0°C. This process is summarised in Figure 6.4.2.

Figure 6.4.2



In contrast, the modification procedure described in Section 3.2.3.II consisted of one stage only, that is, the treatment of Raney nickel with a solution of tartaric acid and sodium bromide at a temperature of 100°C. This process is summarised in Figure 6.4.3.

Figure 6.4.3



It seemed reasonable to expect that the two methods of catalyst modification shown in Figures 6.4.2 and 6.4.3 would produce catalysts with very similar, if not identical, properties. The effect of varying the pH of the modifying

solution, with 1M aqueous sodium hydroxide, on the behaviour of catalysts *MRNi/NaBr - I and *MRNi/NaBr - II is illustrated in Figures 6.4.4 and 6.4.5 respectively.

Perhaps the feature with greatest impact in Figure 6.4.4 is the appearance of non-zero values for the enantioselectivity. Two maxima of different magnitudes are shown, with the optimum enantiomeric excess of -50% occurring at pH 5.1. It is also obvious that enantiomeric excess and percentage conversion follow opposite trends - as one increases the other decreases; in particular, conversion reaches a maximum of 35% in the absence of any enantioselectivity, at pH 11.0.

The phenomenon of two maxima in the values for enantiomeric excess is repeated in Figure 6.4.5 but, in contrast, the optimum value occurs at a different pH from that in Figure 6.4.4. As before, enantiomeric excess and MAA conversion follow opposite trends. In this case, the maximum conversion of 65% is attained at pH 7.0, but again, no enantioselectivity was observed.

Clearly, the two methods of modification did not, contrary to expectation, result in catalysts with identical properties. It is important, however, to be able to attribute the enantioselectivity which had been obtained to either the presence of the alkali halide co-modifier or to the increased temperature of modification - or in part, to each, as it was not possible to distinguish between the two effects from the

Figure 6.4.4

Percentage Conversion / Enantiomeric Excess v pH of Modifying Solution

for MAA $\xrightarrow[H_2]{*MRNi/NaBr}$ MHB

(3g MAA/0·45g catalyst in 25ml toluene; reaction temp. = 70°C)

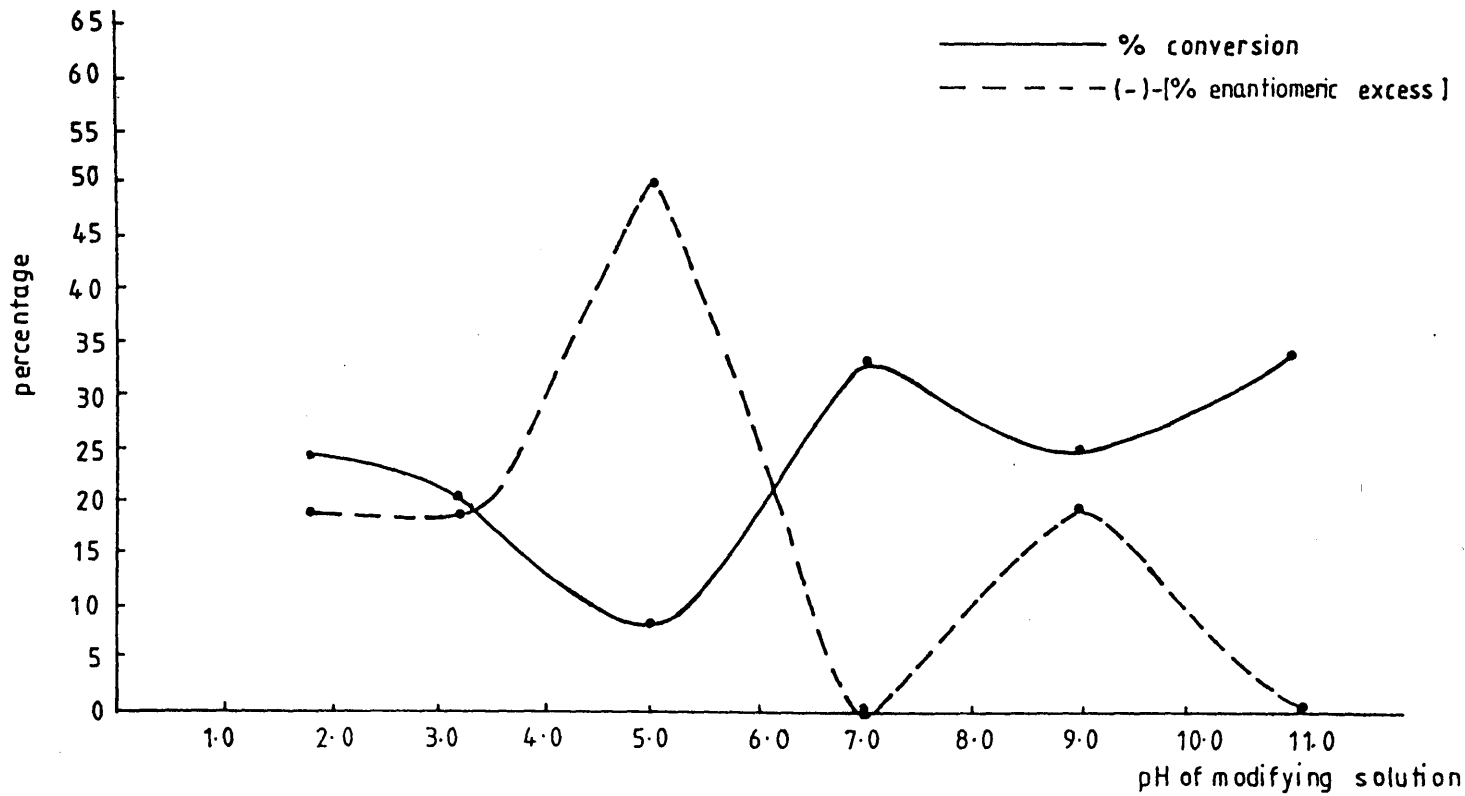
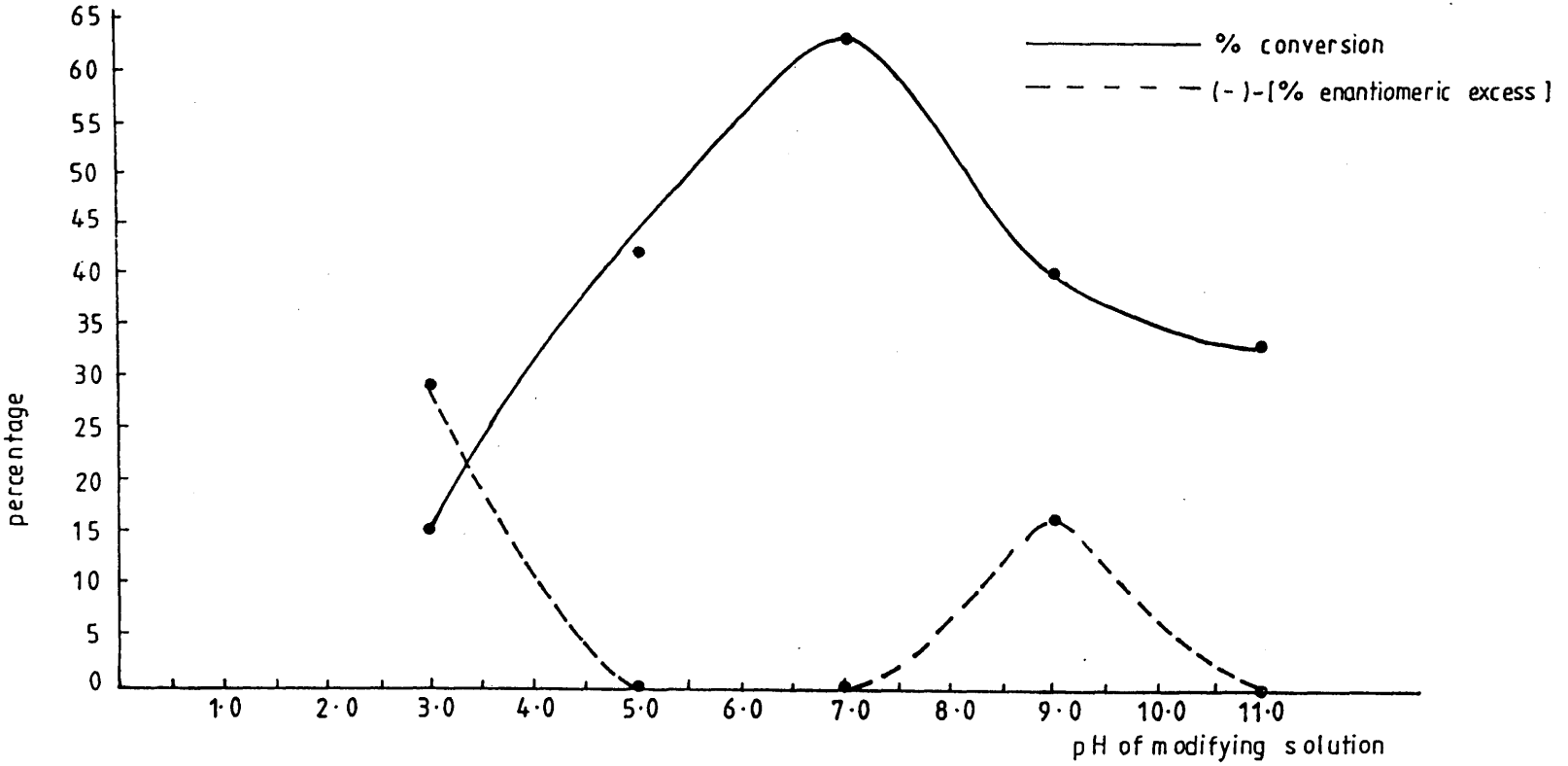


Figure 6.4.5

Percentage Conversion / Enantiomeric Excess ν pH of Modifying Solution

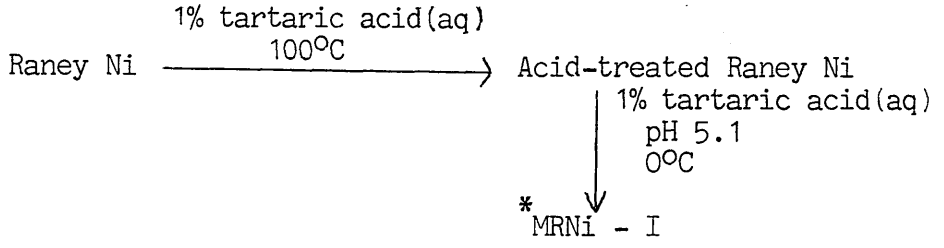
for MAA $\xrightarrow[H_2]{*MRNi/NaBr}$ MHB

(3g MAA/0·45g catalyst in 25ml toluene; reaction temp = 70°C)



experiments carried out. In order to achieve this distinction it was necessary to conduct a further four experiments and the details of the modification processes for each of the four different catalysts are shown in Figures 6.4.6 to 6.4.9. In Figure 6.4.6, the preparation of catalyst *MRNi - I is described.

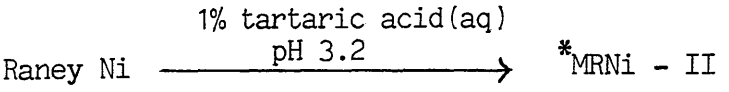
Figure 6.4.6



Thus, the preparation of catalyst *MRNi - I was identical to that of *MRNi/NaBr - I which had been found to result in maximum enantioselectivity, with the exception that, in the former case, tartaric acid was the only modifying agent used.

The preparation of catalyst *MRNi - II is summarised in Figure 6.4.7

Figure 6.4.7



Catalyst *MRNi - II, therefore, was prepared in a manner identical to that of *MRNi/NaBr - II which was observed to result in maximum enantiomeric excess of MHB, with the

exception that, in the former case, tartaric acid was the only modifying agent present.

Finally, the details of the modifying procedures for catalysts RNi - I and RNi - II are shown in Figures 6.4.8 and 6.4.9 respectively.

Figure 6.4.8

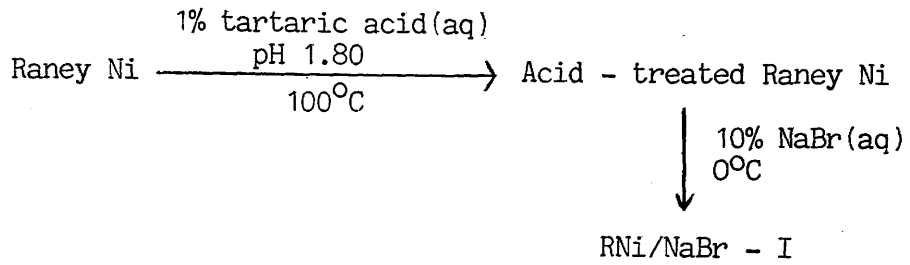
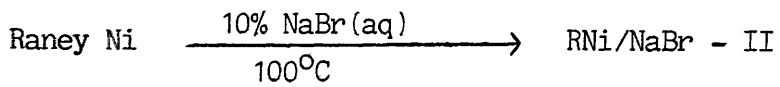


Figure 6.4.9



Thus, the preparations of catalysts RNi/NaBr - I and RNi/NaBr - II were equivalent to those of *MRNi - I and *MRNi - II respectively, with the one exception that sodium bromide was the one modifying agent used, as opposed to tartaric acid. However, in order to avoid the addition of any foreign ionic species, the pH of the sodium bromide modifying solutions was not altered from the value of 7.0.

The six catalysts, the behaviours of which are to

be compared, are listed in Table 6.4.2, together with the main features of each individual modification process.

Table 6.4.2

Catalyst	No. stages in modification	pH of modification	Presence of modifiers	
			Tartaric Acid	NaBr
*MRNi/NaBr - I	2	5.1	Yes	Yes
*MRNi/NaBr - II	1	3.2	Yes	Yes
*MRNi - I	2	5.1	Yes	No
*MRNi - II	1	3.2	Yes	No
RNi/NaBr - I	2	7.0	No	Yes
RNi/NaBr - II	1	7.0	No	Yes

Table 6.4.3 is a list of the results obtained from using each of the six catalysts in the hydrogenation of MAA.

Table 6.4.3

Catalyst	Conversion (%)	-(Enantiomeric Excess)(%)
*MRNi/NaBr - I	8	50
*MRNi/NaBr - II	15	29
*MRNi - I	27	32
*MRNi - II	30	0
RNi/NaBr - I	32	0
RNi/NaBr - II	29	0

(3.0g MAA/0.45g catalyst in 25ml toluene)

Thus, the effects of sodium bromide, tartaric acid and temperature of and number of steps in the modification of the catalyst could be established.

The enhancement in optical yield found on using an alkali halide as a co-modifier was initially surprising by virtue of the simple fact that there could be no chirality inherent in the ionic salts which were found to be effective. This was reflected in the nature of the discovery of the enhancement, which was purely coincidental. While investigations on modified Raney nickel catalysts were being carried out in Japan during the summer of 1978, the supplied water, which was used to make aqueous solutions of the asymmetric catalyst modifier, became "polluted" with ions such as SO_4^{2-} and Cl^-. It was soon realised that the presence of ions such as these was advantageous and, by means of further related studies, the excellence of sodium bromide as a co-modifier was discovered.[113] However, it can be seen from Table 6.4.3 that neither catalyst RNi/NaBr - I nor RNi/NaBr - II is enantioselective and so it is concluded that the achiral sodium bromide in isolation does not bestow any asymmetric activity upon the Raney nickel catalyst; this was apparently the first time that any experiments using sodium bromide instead of, as opposed to in conjunction with, tartaric acid had been carried out. Therefore, sodium bromide must function with tartaric acid in order to be effective. The only other firm conclusion which can be

made from Table 6.4.3 involved the results for catalysts *MRNi/NaBr - I and *MRNi - I (or alternatively, *MRNi/NaBr - II and *MRNi - II). Thus, the presence of sodium bromide causes a decrease in the conversion of MAA; once again, however, this was only found to occur when sodium bromide was used in conjunction with tartaric acid, as relatively high conversions were obtained using catalysts RNi/NaBr - I and RNi/NaBr - II.

The problem which remained was the clarification of the effect of raising the temperature of modification. It was notable that a value of zero for the enantiomeric excess was obtained for catalyst *MRNi - II. This result is entirely consistent with Figure 6.4.1, in which the enantioselectivity remains at zero, regardless of the modifying pH. Since the modifying temperature was 100°C in the former case compared with 0°C in the latter, an increase in the modifying temperature alone is not sufficient if enantioselectivity is to be achieved. Neither is there much alteration in the conversion of MAA, which was around 30% in each case. This finding is not consistent with Tatsumi's observation of an increased asymmetric activity with a simultaneous increase in modifying temperature.[66]

However, a significant optical yield is obtained on using catalyst *MRNi - I and so this result further reflects the importance of the nature and number of steps in the modification procedure. Since the second step is

identical to the preparation of the *MRNi catalyst used to produce the results shown in Figure 6.4.1, it followed that a closer examination of the first step was necessary. This consisted of the treatment of Raney nickel with an aqueous solution of tartaric acid at 100°C, which involved the removal of residual aluminium metal as water - soluble aluminium chelates. In view of the value of -50% found for the enantiomeric excess, at pH 5.1, it is concluded that the high temperature acid treatment had a favourable effect. However, in contrast to Izumi's findings[68], this gain in enantioselectivity occurs with a simultaneous loss in hydrogenation activity as, in order to obtain maximum enantioselectivity, a conversion of less than 10% was obtained.

The enhancement found on removing aluminium from the catalyst was also consistent with a report made by Gross and Rys,[149] in which it was stated that optical yield was lowest with a Raney nickel containing a relatively large amount of aluminium, and vice versa. One suggestion as to the reason for this detrimental behaviour of aluminium was that, since most was present as alumina, hydration of aluminium oxide occurred and so surface hydroxyl groups were attached to aluminium atoms on the metal surface. It was thought that these surface hydroxyls interfered with the adsorption of MAA on enantioselective sites and so the asymmetric activity of the catalyst was lowered. In relation

to this, Hoek and Sachtler[65] found that the use of alumina as a support for a nickel catalyst resulted in a lowering of asymmetric activity. Their interpretation was that non-selective hydrogenation could be occurring on the alumina surface. The latter explanation is consistent with the fact that a decrease in conversion is found on removing aluminium from the Raney nickel catalyst. If the former explanation were correct, no change in conversion would have been expected. However it is impossible to make any firm conclusion regarding the role of aluminium, since its removal was not the only alteration in the catalyst effected by high temperature acid treatment. On the contrary, a certain amount of corrosion to form Ni^{2+} cations was evident from the strong green colour which gradually appeared and so some alteration in the surface and perhaps also in the bulk, was occurring.

Having discussed the role of sodium bromide, modifying temperature and the aluminium content of catalysts, another factor concerning Figures 6.4.4 and 6.4.5 which must be considered is the effect of pH. It is seen from each of these figures that the modifying pH affects both conversion and enantioselectivity, although slightly different effects are obtained for different methods of catalyst modification. The exact nature of the tartrate species contained in an aqueous solution of tartaric acid is dependent on the pH and the acid itself, which is dibasic, has pK_a values of 2.34 and 4.98 respectively. Thus, at

pH values below 2.34 tartaric acid itself will be the predominant tartrate species while sodium tartrate, $(Na^+)_2C_4H_4O_6^{2-}$, will predominate at pH values greater than or equal to 4.98. At pH values intermediate between the two extremes, the species which will predominate is sodium hydrogen tartrate, $Na^+HC_4H_4O_6^-$. In reports by Izumi[55] and Yasumori[150] it was found that the optimum pH was 5.0 - 5.1 and so it was concluded that the effective form of the modifier was the dianion, present as sodium tartrate. According to Fish and Ollis[67] a value of around 5 for the pH corresponded to an intermediate surface coverage of modifier. However, variations in the value of the optimum pH have been found. For example, Izumi[68] reported that using a catalyst identical to *MRNi/NaBr - II, the preparation of which is shown in Figure 6.4.3, maximum enantioselectivity occurred at pH 3.2. In contrast, Klabunovskii[69] found two maxima in enantiomeric excess which corresponded to pH values of 2 and 13 respectively. The results shown in Figures 6.4.4 and 6.4.5 are in some way consistent with all of these reports. First, the occurrence of two maxima in both cases is in agreement with Klabunovskii's findings, although there is a discrepancy between the corresponding pH values. Second, the greatest enantiomeric excess in Figure 6.4.4 occurs around a pH value of 5, which is in accordance with the similar results found by Izumi and Klabunovskii. Lastly, a modifying solution of approximately pH 3 resulted in the greatest enantiomeric excess in Figure 6.4.5; since the catalyst used to produce the results in

this figure was *MRNi/NaBr - II, an optimum pH of around 3 was in exact agreement with Izumi's observations using the same catalyst. The two most important questions concerning the effect of pH in Figures 6.4.4 and 6.4.5 are:-

(i) Why is there the occurrence of two maxima at two particular pH values?

(ii) What are the reasons for the discrepancy between the pH values at which these two sets of maxima occur?

The variation of enantioselectivity with pH is not initially surprising, since it is to be expected that the extent to which tartaric acid is absorbed, as well as the nickel-tartrate complex formed, will vary according to which tartrate species is present in the modifying solution. On considering the two maxima at or below pH 5, it is concluded that the most effective form of the modifier must be the dianion and monoanion in Figures 6.4.4 and 6.4.5 respectively.

The reason for the occurrence of maxima around pH 8 - 9 is less clear, since there is no change in the ionic form of the tartrate beyond pH 5. It is assumed, therefore, that the presence of alkali ions must have some influence, since the concentration of hydroxide ions in the modifying solution will increase as the pH increases from 7 upwards. It then follows that there must be some optimum $[OH^-]$ which occurs at pH 8 - 9. Referring once more to investigations by Fish and Ollis,[67] the modifier surface coverage was found to decrease with increasing pH and, in

fact, was calculated to be extremely low at pH 8 - 9. However, these results were found in conjunction with maximum optical yield occurring at pH 5 (that is, the pH which corresponded to an intermediate surface coverage) and so it is unlikely that the exact values calculated for surface coverage will prove to be useful in attempts to explain the appearance of maxima at significantly higher pH values. In spite of this, the general trend of surface coverage with pH is consistent with the results shown in Figures 6.4.4 and 6.4.5. Considering, first, Figure 6.4.4; the magnitude of the enantiomeric excess at pH 9 is less than that at pH 5 and, in addition, the conversion at pH 5 is less than that at pH 9 - both of these results would be expected if less tartaric acid were actually present on the surface of the catalyst as the pH increased.

With reference to the second question concerning the effect of pH - that is, the reasons for the discrepancy between the pH values at which the maxima in Figures 6.4.4 and 6.4.5 occur - attention must be focussed on the differences between the modifications of the catalysts used to produce the two sets of results. These two types of catalysts will be referred to as type -I and type -II respectively since the preparation of each is described in Section 3.2.3 I and II respectively.

Since the initial step in the production of type -I catalyst was treatment at high temperature with a

solution of tartaric acid, the catalyst surface was already corroded when the modifying solution was added. In contrast, the surface of type -II catalyst had not been subjected to any corrosion process before modification was carried out. Thus, the Raney nickel catalysts presented to a solution of tartaric acid and sodium bromide could not be identical. Furthermore, if maximum surface coverage does occur at minimum pH, it would be expected that high temperature treatment with tartaric acid would result in almost complete coverage of the metal surface with tartaric acid molecules after the removal of aluminium and some surface corrosion had been effected. In the event of this "poisoned" catalyst coming in contact with the modifying solution, an equilibrium between adsorbed and dissolved tartaric acid would be established. The net effect of this equilibrium would be that, above a certain minimum pH, a certain amount of tartrate is removed from the catalyst and so sites for the adsorption of MAA would become available. This is consistent with the finding that maximum optical yield was obtained at a higher pH in the case of the type -I catalyst. For the two types of catalyst, therefore, there would be a difference in the concentration of tartrate species present in the modifying solutions in which the catalysts were immersed and this difference in tartrate concentration would persist, regardless of the modifying pH. It is probable that this difference would result in the second, lower maximum in enantiomeric excess occurring at different pH values.

The general trend that enantiomeric excess decreased as conversion increased, and vice versa, is seen in both Figure 6.4.4 and 6.4.5. There are several possible reasons for this behaviour. One is that optical yield is a function of conversion. Investigations of the relationship between the two have been carried out by Gross and Rys[149] and, certainly, some influence of conversion on optical yield was observed. Although the results varied according to which particular Raney alloy was used as the starting material in the preparation of the modified Raney nickel catalyst, an increase in the conversion from 0 to 20% resulted in an increase in optical yield to a maximum value, which was maintained until the conversion reached about 70%. In contrast, a sharp decrease in optical yield was observed as the conversion proceeded towards 100%. A closer examination of the conversion values in Figures 6.4.4 and 6.4.5 reveals that the range is from 0 to a maximum of about 35 and 30% respectively. It follows that the low enantiomeric excesses obtained at conversions at or below 35%, that is, values significantly less than 70%, cannot be attributed simply to a relationship between the two. Furthermore, neither can the occurrence of a relatively large enantiomeric excess be caused by the corresponding conversion, since, according to Gross and Rys, the maximum optical yield attained at or below conversions of 20% did not decrease at all until conversions greater than 70% were reached. Thus, the theory that the modifying pH affects

only the conversion and that variations in the enantiomeric excess are merely a consequence of variations in conversion can be discarded.

An alternative explanation is that the enantioselectivity reflects the amount of modifier present on the catalyst surface. If this were the case a relatively large amount of modifier is adsorbed when maximum enantioselectivity occurs and so there are relatively few catalytic sites available for the purpose of non-selective hydrogenation of MAA; the consequence of such a situation would be a drastic reduction in the overall conversion. This theory assumes that the rate constants for selective and non-selective hydrogenation are more or less equal. If, in contrast, the latter were much greater than the former, there would be no requirement for a reduction in the amount of racemic MHB produced, simply because of a shortage of unmodified nickel sites. Enantioselectivity cannot reflect the amount of modifier present on the surface completely, since, at low pH, Fish and Ollis[67] found surface coverage to be maximised when only a very low optical yield was obtained; the results in Figures 6.4.4 and 6.4.5 are consistent with the latter finding. Nonetheless, the general idea that enantioselectivity occurs at the expense of conversion is important.

A further point which is related to this theory concerns the rate at which MHB is desorbed from enantio-

selective sites and this is discussed in Chapter 7.

6.5 Digestion Temperature

The effect of varying the temperature at which nickel:aluminium alloy, the starting material in the preparation of Raney nickel catalysts, was digested with aqueous alkali has also been investigated. The details of the digestion process are described in Section 3.2.1. Studies were made of the effect on both unmodified and modified catalysts and a description of the preparation of these catalysts is given in Table 6.5.1.

Table 6.5.1.

Catalyst	Section or Figure in which modification described	Modification Parameters	
		pH	Temperature (°C)
*MRNi	Section 3.2.1	5.1	0 - 80
*MRNi/NaBr - II	Figure 6.4.7	3.2	0 - 80
*MRNi/NaBr - I	Figure 6.4.6	5.1	0 - 80

The results obtained from altering the temperature of digestion of these catalysts is shown in Table 6.5.2.

Table 6.5.2

Catalyst	Digestion Temperature ($0^{o}C$)	Modification Temperature ($0^{o}C$)	Conversion (%)	-(Enantiomeric Excess)(%)
(a) RNi	80	-	30	0
(b) RNi	0	-	37	0
(c) *MRNi	0	0	25	0
(d) *MRNi	0	80	17	0
(e) *MRNi	80	0	15	0
(f) *MRNi	80	80	45	21
(g) *MRNi	40	40	24	0
(h) *MRNi/NaBr-II	0	80	15	28
(i) *MRNi/NaBr-II	80	80	31	26
(j) *MRNi/NaBr-II	40	40	25	0
(k) *MRNi/NaBr-I	0	80	9	44
(l) *MRNi/NaBr-I	80	80	7	0

(3.0g MAA/0.45g catalyst in 25ml toluene)

It has been shown previously that an increase in either the temperature at which Raney alloy is digested or the duration of the treatment with alkali results in a larger amount of aluminium being removed.[116]

When the aluminium content of Raney alloy is decreased, the structure of the resulting Raney nickel catalyst is altered in two ways. First, the proportion of the total metallic surface area which is aluminium is decreased and, second, the creation of a greater number of pores in the nickel which remains causes an increase in the total surface area of nickel; this results in an increase in the number of nickel atoms which can function as catalytic sites, provided the radii of the newly created pores are sufficiently large for the diffusion of MAA molecules into these pores to occur. However, it must also be considered that, since the means of decreasing the aluminium content of catalysts used in the experiments described in this section was an increase in digestion temperature, some coalescence of nickel particles may have occurred. The precise relationship between the hydrogenation activity of the catalyst digested at a higher temperature and that of the catalyst prepared at a lower temperature would depend both on the relative amounts of aluminium contained in the catalysts and the degree to which coalescence of nickel particles had occurred.

On comparing reactions (a) and (b) in Table 6.5.2 it is seen that an increase in digestion temperature resulted in a lowering of the conversion of MAA for unmodified Raney

nickel, RNi. A similar trend in conversion was also observed for the modified catalysts *MRNi, when modified at a temperature of 0°C, and *MRNi/NaBr-I by comparing reaction (c) with (e) and (k) with (l) respectively. These results are consistent with the theory that the numbers of active sites in the catalyst available for hydrogenation has decreased as a result of nickel particle coalescence. The opposite trend is seen for catalysts *MRNi/NaBr-II and *MRNi, when modified at 80°C, by comparing reactions (d) with (f) and (h) with (i) respectively - that is, an increase in conversion is observed as the digestion temperature is increased. No explanation can be offered for the fact that these two, opposing trends had been observed.

The effect of digestion temperature on enantiomeric excess is also of interest. For catalyst *MRNi, reactions (c) and (e) show that an increase in digestion temperature, while the modifying temperature remains fixed at 0°C, did not produce any enantioselectivity. In contrast, reactions (d) and (f) show that an increase in the temperature of digestion while that of modification is 80°C resulted in the observation of a non-zero enantiomeric excess. Although opposing trends in conversion are observed for catalysts *MRNi/NaBr-I and *MRNi/NaBr-II, a certain similarity exists between the trends for enantiomeric excess. However, while there is a drastic decrease in enantioselectivity with an increase in digestion temperature in the case of the former catalyst, only a very slight decrease occurs in the case of the latter. No enantioselectivity is observed when the digestion and modification

temperatures were both fixed at 40°C, that is, between the extremes of 0 and 80°C, regardless of whether the catalyst was *MRNi or *MRNi/NaBr-II, as seen from reactions (g) and (j).

A further point of interest which arises from Table 6.5.2 is the variation in the effectiveness of sodium bromide as a co-modifier with a change in the temperature of alloy digestion. From entries (d) and (h) it is seen that a significant improvement in the enantioselectivity occurs on changing the catalyst from *MRNi to *MRNi/NaBr-II when the digestion temperature was 0°C; a similar effect is observed when catalyst *MRNi is replaced by *MRNi/NaBr-I, as seen from reactions (d) and (k). Contrary to this, when the digestion temperature was 80°C, the presence of sodium bromide had apparently very little effect on the enantioselectivity when catalyst *MRNi/NaBr-II was used, as seen from reactions (f) and (i), while catalyst *MRNi/NaBr-I did not possess any enantio-differentiating ability at all, as seen from reaction (l); on comparing reactions (f) and (l) it is apparent that the presence of sodium bromide had a detrimental effect on the asymmetric activity of the modified catalyst.

The idea that the presence of aluminium is considered to have a damaging effect on the enantio-differentiating ability of modified Raney nickel catalysts is discussed in Section 6.4; it follows that an enhancement in enantioselectivity would be expected if the digestion temperature were increased. Thus, some of the results shown in Table 6.5.2 are consistent with this expectation,

and therefore also with results obtained by Izumi et.al.,[83] while others are not. It is notable that the catalysts which had been co-modified with sodium bromide suffered a loss in asymmetric activity, in spite of aluminium having been removed from the metal itself. This observation will be referred to in a later discussion on the role of sodium bromide in the determination of catalyst enantio-selectivity.

Despite the variation of temperatures of modification and digestion producing some very interesting results, success in carrying out the hydrogenation of MAA, which, simultaneously produced MHB in high yield and with reasonable enantioselectivity was not achieved. The maximum enantiomeric excess which had been obtained was -50%, which occurred in conjunction with a conversion of only 8%, as seen in Figure 6.4.4 when the modifying pH was 5.1. This result, together with reactions (k) and (l) in Table 6.5.2, illustrates that, when modification was carried out as described in Section 3.2.3.I, the catalyst which was produced had a very low activity for hydrogenation, regardless of the digestion temperature of the Raney alloy.

When the modifying procedure was as described in Section 3.2.3.II, the catalyst which was produced did not possess maximum enantio-differentiating ability; however, its greater activity was reflected in a conversion of 15%, as opposed to only 8%. The activity of this catalyst could be further increased by raising the digestion temperature from 0 to 80°C, as seen from reactions (h) and (i) in Table

6.5.2. For this reason, the Raney nickel catalyst used to obtain the results in Section 6.6 was *MRNi/NaBr-II; that is, the catalyst preparation followed was that described in Section 3.2.3.II, with the modifying pH fixed at 3.2.

The digestion temperature of the Raney alloy starting material was fixed at 100°C, in order to maximise the conversion of MAA during hydrogenation reactions.

The surface areas of the RNi and *MRNi/NaBr-II catalysts, using a digestion temperature of 100°C in each case, were determined by the B.E.T. method, with nitrogen as the adsorbate gas and the respective results were 97.742 and 79.773 m^2g^{-1}. Thus, the modification process had resulted in a decrease in catalyst surface area. This decrease is attributed to either a growth in nickel particle size or, alternatively, a decrease in pore volume; the latter explanation is preferred, since it is highly possible that adsorbed tartaric acid molecules could hinder the entry of nitrogen adsorbate molecules into the catalyst pores.

6.6 Effect of Hydrogen Pressure.

The apparatus used for high pressure liquid phase hydrogenation reactions is shown and described in Figure 3.4.1.1 and Section 3.4.1 respectively. The effect of increasing the pressure under which MAA was hydrogenated, in the presence of catalyst *MRNi/NaBr-II, is shown in Table 6.6.1; the procedure for high pressure hydrogenation is described in Section 3.4.2.

Table 6.6.1

Initial Pressure of Hydrogen (atm.)	Conversion (%)	-(Enantiomeric Excess) (%)
1	35	25
90	80	55

(11.5ml MAA/0.90g catalyst in 23ml toluene; reaction temperature = 70°C)

It is seen from Table 6.6.1 that an increase in hydrogen pressure produced an increase in conversion as well as in enantiomeric excess. The former result is consistent with there being a greater availability of hydrogen at the catalyst surface as the pressure of the gas is increased.

The method of preparation of each of the two catalysts used in the two reactions was the same and so it is expected that the resulting catalysts were very similar, if not identical. This means that the nature and number of nickel-modifier/co-modifier complexes which were present during the two hydrogenation processes were also very similar. In view of this, it is expected that the effect of hydrogen pressure would simply be to increase the overall rate of hydrogenation. However, the results in Table 6.6.1 are not consistent with this expectation. On increasing the conversion from 35 to 80%, the (R):(S) ratio of MHB produced is in fact more than doubled. This means that the increase in hydrogen pressure resulted in a drastic alteration in the enantio-differentiating ability of the catalyst in favour of the production of the 'R' enantiomer of MHB. The conclusion

must be that the processes which result in the formation of (R)- and (S)- MHB must have different dependencies on the concentration of hydrogen which is present at the surface of the catalyst, since it is the value of this concentration which is controlled by the pressure of hydrogen which is used in the reaction.

It is seen from Table 6.3.2 that the choice of solvent had a considerable effect on the conversion of MAA in atmospheric pressure hydrogenations and a similar set of investigations has been carried out for reactions at high pressure. The results obtained from using some of the solvents listed in Table 6.3.3, that is, solvents varying widely in dielectric constant, are shown in Table 6.6.2.

Table 6.6.2

Solvent	Conversion (%)	-[Enantiomeric Excess] (%)
Toluene†	80	55
Methyl propionate	95	82
Methyl acetoacetate	85	69
Butanol	100	85
N,N-Dimethyl formamide	5	0

(†:- Traces of methyl cyclohexane found in reaction mixture, following hydrogenation of MAA).

(11.5ml MAA 10.90g catalyst in 23ml solvent; reaction temperature = 70°C; initial H_2 pressure = 90 atm.)

It is clear from Table 6.6.2 that a remarkably poor conversion was obtained on using N,N-dimethyl formamide, the

dielectric constant of which is extremely large. This lack of reaction of MAA is almost an exact repetition of the result obtained when an atmospheric pressure of hydrogen was used, as seen from Table 6.3.2. Another factor which may have been involved concerns the relative solubility of hydrogen in different solvents; an extremely low solubility of hydrogen gas in N,N-dimethyl formamide would, to some extent, account for the low conversions of MAA obtained. In any case, an increase in hydrogen pressure had a negligible effect.

It is also seen from Table 6.6.2 that significantly higher conversions were obtained using solvents other than N,N-dimethyl formamide. Thus, solvents with less extreme values of dielectric constants proved to be more useful for reaction purposes. A contributing factor may have been that the solubility of hydrogen was greater in solvents such as butanol and methyl propionate than in N,N-dimethyl formamide. Furthermore, on comparing Tables 6.3.2 and 6.6.2, it is evident that an increase in gas pressure produced a drastic increase in conversion, regardless of the precise identity of the solvent. Thus, factors which appear to control the extent of reaction in Table 6.3.2, such as the rate at which hydrogen diffuses through a particular solvent, become less important when the amount of hydrogen present within the reaction vessel is increased.

An entirely different aspect of the role of solvent molecules is found to arise in the case of toluene. Gas chromatographic analysis confirmed that, when toluene was

used as the reaction solvent, trace amounts of methyl cyclohexane appeared in the reaction mixture, following the hydrogenation of MAA - that is, hydrogenation of toluene solvent molecules must have been occurring. It is therefore highly probable that toluene molecules were actually poisoning the catalyst surface, thereby inhibiting the reduction of MAA to some extent; this is reflected in a conversion of only 80%, a value lower than that obtained on using some of the other solvents listed in Table 6.6.2. No comparable observations were made with any other solvents and so no evidence was obtained to suggest that any further examples of catalyst poisoning by solvent molecules were extant. Thus, toluene was not considered to be a suitable solvent for hydrogenation reactions.

A further point from Table 6.6.2 is that a reasonably high conversion was obtained when the reaction was carried out in the absence of any added solvent - that is, when MAA itself was the reaction solvent. Although this is not the highest value of conversion listed, it is considerably greater than the corresponding value of only 4% in Table 6.3.2. Also, in contrast to reactions performed at atmospheric pressure, there was a complete lack of any evidence for the occurrence of catalyst corrosion by MAA, since no colouration of the reaction mixture was observed. However, it is also clear from Table 6.6.2 that the most efficient way of performing liquid phase hydrogenation reactions was in the presence of an added solvent, such as methyl propionate or butanol. Consequently, in subsequent

investigations, either of these was used as the reaction solvent, in conjunction with a reaction temperature of 70°C and an initial hydrogen pressure of 90 atm.

In view of the reports mentioned in Section 1.7.3[79], which claim that improvements in enantioselectivity are achieved by the addition of a small amount of an organic acid to reaction mixtures, the effect of both acidic and basic additives was investigated. The results are shown in Table 6.6.3.

Table 6.6.3.

Additive	Volume of Additive (ml)	Conversion (%)	-[Enantiomeric Excess] (%)
-	-	95	82
Acetic acid	0.2	90	62
Acetic acid	2.0	86	0
Pyridine	0.2	27	0

(11.5ml MAA/0.90g catalyst in 23ml methyl propionate).

No enhancement in enantioselectivity was obtained with either an acidic or a basic additive - on the contrary, both proved to have a detrimental effect on both the conversion and enantiomeric excess. The effect of small amounts of pyridine is seen to be more damaging than that of acetic acid. This is possibly caused by pyridine molecules, which are behaving as an extremely effective catalyst poison. This is consistent with the suggestion, made earlier in this section, that toluene molecules could be adsorbed on to the nickel

surface, thereby blocking sites normally active in MAA hydrogenation. It is likely that pyridine molecules will be more easily adsorbed than toluene molecules since they have two sites for coordination; as well as an aromatic ring, a pyridine molecule also possesses a basic nitrogen atom. Several active sites on the catalyst surface would be very effectively poisoned by the adsorption of only one pyridine molecule, positioned in such a way that the aromatic ring was parallel to the metal surface. This would explain the sharp decrease in the hydrogenation activity of a nickel catalyst on the introduction of relatively few pyridine molecules into the reaction mixture. It is also conceivable that, as a result of the sheer bulk of an aromatic ring, the stereochemistry of nickel-modifier/co-modifier complexes would be greatly disturbed if a molecule of pyridine were to be adsorbed on to a neighbouring nickel atom. Since the expected consequence of such an occurrence would be a decrease in the enantiomeric excess obtained using this poisoned catalyst, a satisfactory explanation is thus provided for the zero value of enantiomeric excess in Table 6.6.3. In view of this zero value of optical rotation which was obtained, there is no evidence to suggest that the action of the pyridine molecules was to displace dextrorotatory tartaric acid molecules from the surface of the catalyst; if any such displacement had occurred, the solution of the reaction mixture would have produced a positive optical rotation.

It is seen from Table 6.6.3 that the presence of

acetic acid molecules caused only a slight decrease in conversion while simultaneously affecting the enantiomeric excess to a much larger extent. This suggests that the acid molecules themselves did not poison sites for hydrogenation, but instead were interacting with nickel-modifier/co-modifier complexes (or, alternatively, nickel-substrate complexes) in such a manner as to interfere strongly with the chiral "template" effect of the adsorbed tartrate species. One consequence of adding acetic acid (or pyridine) molecules to a reaction mixture is that the pH of the solution which is in contact with the catalyst surface would be altered. It is therefore possible that a change in the ionic form of at least some of the tartrate species could occur, for example

$$[HC_4H_4O_6]^-_{(ads)} \xrightarrow{H^+} [H_2C_4H_4O_6]_{(ads)}$$

In this way, $[HC_4H_4O_6]^-$ ions, which, as discussed in Section 6.4, are considered to be the effective form of the modifier when the catalyst is modified at a pH of 3.2, are converted to adsorbed tartaric acid species, which were found to have little effect on the enantio-differentiating ability of Raney nickel catalysts. Consequently, the enantioselectivity of the catalyst would be drastically reduced, while the overall conversion would remain almost totally unaffected.

The most important conclusion which can be made from the results in Table 6.6.3 is that, contrary to other reports,[79]

no enhancement was obtained with either an acidic or a basic additive and, therefore, no such additives were included in future reactions.

Following the discovery that the enantioselectivity and conversion in reactions were greatly improved when the initial hydrogen pressure was increased from 1 to 90 atm., the effect of using pressures between these two extremes was also investigated. The results are shown in Figure 6.6.1.

It is seen from Figure 6.6.1 that there was virtually no change in either the conversion or the enantiomeric excess between pressures of 5 and 90 atm; the sharp increase for both occurs in the range of 1-5 atm. Thus, the crucial change in hydrogen concentration at the catalyst surface which results in the significant enhancements seen in Figure 6.6.1 must be occurring between the pressures of 1 and 5 atm.

The effect of varying the reaction temperature has also been investigated, and the results obtained are shown in Figure 6.6.2. It is seen that conversion and enantiomeric excess follow similar trends in that both increase as the reaction temperature approaches 60-70^{o}C. However, enantiomeric excess attains its maximum value at a temperature of 70^{o}C and then gradually decreases, while the conversion is maintained at 100%, provided the reaction temperature is at or above 60^{o}C. The results for enantiomeric excess are similar to those obtained by Izumi *et al.*[72], shown in Figure 1.7.3.1; however, in the latter set of results the maximum was more pronounced and corresponded to a reaction temperature of about

Figure 6.6.1 Effect of Hydrogen Pressure on

$$MAA \xrightarrow[H_2]{*MRNi/NaBr} MHB$$

(11·5ml MAA/0·90g catalyst in 23ml butanol; reaction temp. = 70°C)

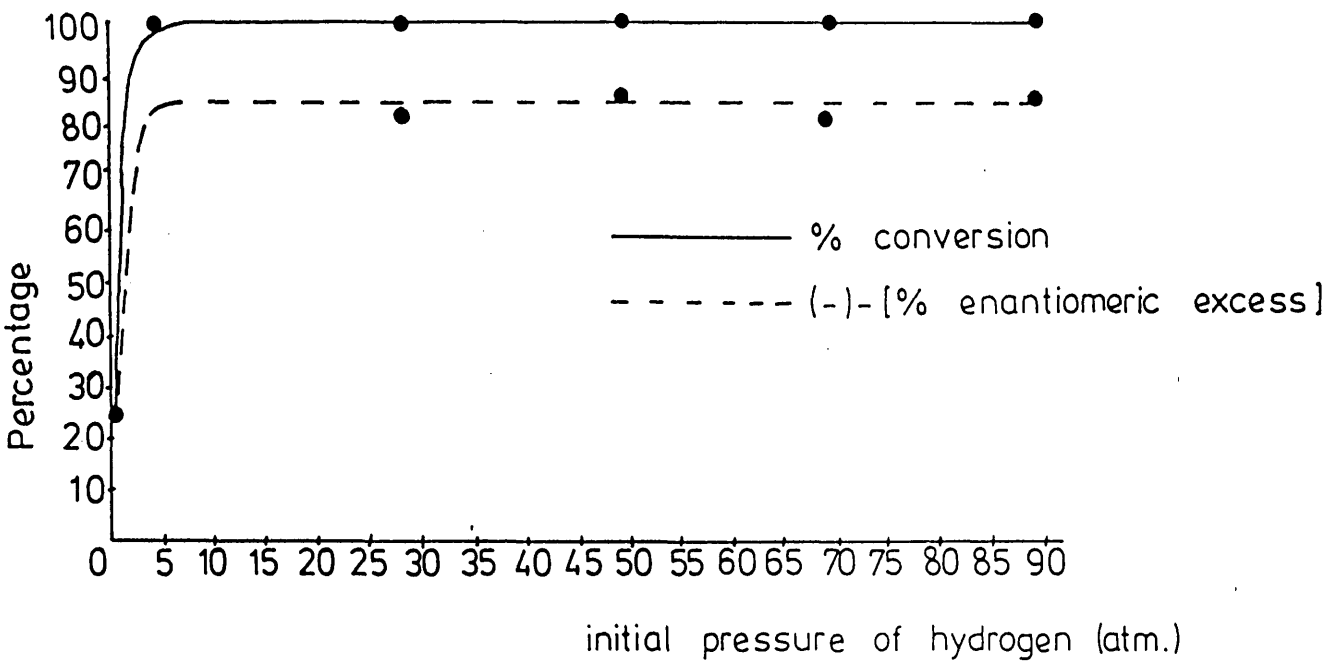
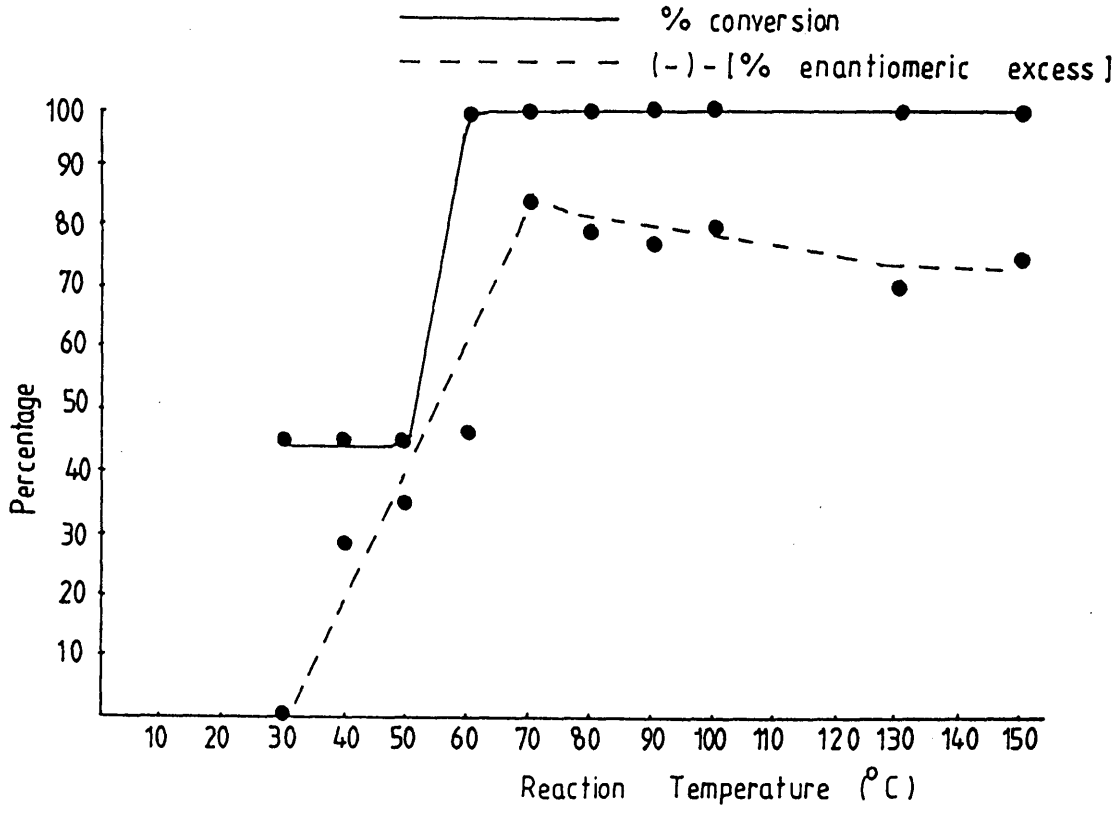


Figure 6.6.2 Effect of Reaction Temperature on

$$MAA \xrightarrow[H_2]{*MRNi\ /NaBr} MHB$$

(11·5ml MAA / 1 90g catalyst in 23ml butanol; initial H_2 pressure = 90 atm.)

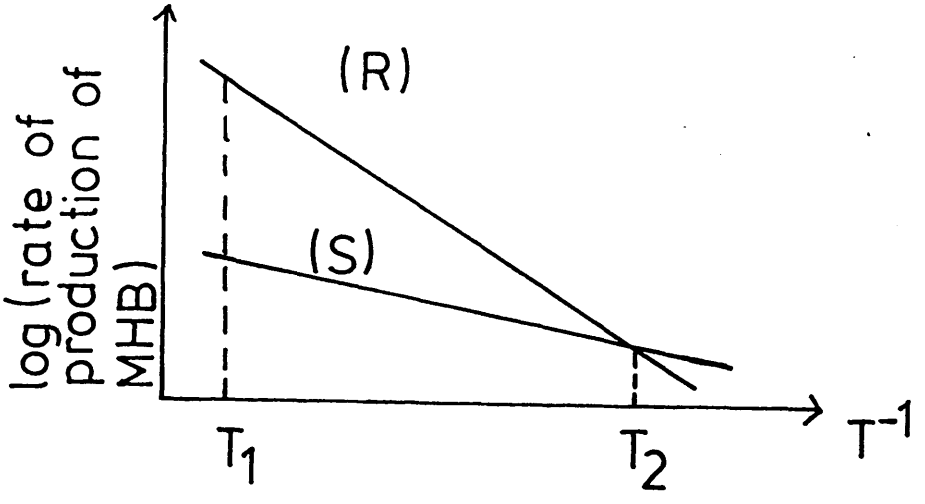


50°C. Izumi's suggestion was that, at temperatures beyond 50°C, tartaric acid no longer possessed the ability to form hydrogen bonds with the substrate and, consequently, the enantiomeric excess of MHB obtained decreased. However, this theory is not entirely satisfactory when attempts are made to apply it to the results in Figure 6.6.2. Although it is true that a maximum enantiomeric excess is obtained, the curve is far from symmetrical. In contrast to the sharp increase from 0 to -85% between the temperatures of 30 and 70°C, there is only a very slight decrease in enantiomeric excess at temperatures beyond 70°C.

Since the desorption of hydrogen from a metal surface is an endothermic process, any increase in reaction temperature will favour the desorption as opposed to the adsorption of hydrogen. Two other factors which vary with an increase in reaction temperature must also be considered in the case of liquid phase hydrogenation reactions; the solubility of hydrogen in the particular solvent will decrease, whereas the diffusion of hydrogen gas through the bulk solvent will occur at a faster rate. Thus, the change in availability of hydrogen at the catalyst surface with temperature will depend on the net effect of all three processes. If the overall effect is an increase in hydrogen availability, the consequence of an increase in reaction temperature would be identical to that of an increase in the hydrogen pressure - that is, the production of (R)-MHB is favoured relative to that of (S)-MHB, since the former is believed to have a greater dependence on the availability of hydrogen.

An alternative reason for the increase in enantioselectivity with increasing temperature is that the rates of reactions which produce respectively (R)- and (S)-MHB have different temperature dependencies. This situation is represented by two Arrhenius plots in Figure 6.6.3.

Figure 6.6.3



At temperature T_2, the production of (R)- and (S)-MHB would be equally favoured and so no enantioselectivity would be observed. In contrast, at temperature T_1, which is greater than T_2, the production of (R)-MHB is much more favourable than that of (S)-MHB and so a large, negative enantiomeric excess would be obtained. If this is true it is essential that the two Arrhenius plots in Figure 6.6.3 are not parallel. It follows that the activation energies for the production of (R)- and (S)-MHB, $(E_a)_R$ and $(E_a)_S$ respectively, must be different in the sense that

$$(E_a)_R > (E_a)_S$$

6.7 Effect of Conditions of Modification in High Pressure Hydrogenations.

The influence of the pH of the modifying solution and the presence of the co-modifier sodium bromide on the behaviour of Raney nickel catalysts in the atmospheric pressure hydrogenation of MAA is discussed in Section 6.4. In particular, the optimum enantiomeric excess was found to occur at a pH of either 3 or 5, depending on the method of catalyst preparation, while the presence of the co-modifier resulted in an enhancement of enantioselectivity. The effects of these factors have also been investigated for high pressure hydrogenations and the results are shown in Table 6.7.1.

Table 6.7.1.

Catalyst	pH of modifying solution.	Conversion (%)	-[Enantiomeric Excess] (%)
*MRNi/NaBr-II	5.1	100	54
*MRNi/NaBr-II	3.2	100	85
*MRNi - II	5.1	100	19
*MRNi - II	3.2	100	17

(11.5ml MAA/0.90g catalyst in 23ml butanol; reaction temperature = 70°C; initial hydrogen pressure = 90 atm).

It is seen from Table 6.7.1 that maximum conversion was frequently obtained, regardless of the conditions of modification - this is in contrast to corresponding results shown in Table 6.5.2 for atmospheric pressure hydrogenation reactions. It is also clear that sodium bromide had a pronounced influence on

the enantio-differentiating ability of the catalyst; an interesting point is that enantiomeric excesses appeared to be independent of the modifying pH in the absence of any co-modifier, whereas the opposite was true when sodium bromide was included. The catalyst which produced the highest enantiomeric excess of -85% was *MRNi/NaBr-II, when prepared at pH 3.2. This finding is consistent with an earlier observation made by Izumi *et al*.[68]

The highest enantiomeric excess listed in Table 6.5.2 was obtained using catalyst *MRNi/NaBr-I, although the conversion was very low indeed. In view of the excellent conversions listed in Table 6.7.1, the effect of catalyst *MRNi/NaBr-I, prepared at pH 5.1, on the hydrogenation of MAA at high pressure was investigated. However, in spite of attaining a conversion of almost 100%, the corresponding enantiomeric excess was only -65%, a figure much lower than that obtained using catalyst *MRNi/NaBr-II. Consequently, catalyst *MRNi/NaBr-II was used in the experiments which are described in the remainder of this section. It is concluded that, for the hydrogenation of MAA at high pressure, the most effective form of the tartrate modifying agent is sodium hydrogen tartrate, $NaHC_4H_4O_6$. However, little comment can be made regarding the role of sodium bromide - for example, whether it behaves as a selective catalyst poison, or whether its function is to coordinate with adsorbed tartrate complexes - since the conversion was 100%, regardless of whether or not sodium bromide was present.

In order to investigate further the precise role of the sodium and bromide ions, an attempt was made to include it in the reaction mixture, as opposed to having it present in the modifying solution with the tartaric acid. However, a problem was encountered; sodium bromide proved to be insoluble in butanol, the reaction solvent. For this reason, methanol was used instead of butanol and the results are shown in Table 6.7.2.

Table 6.7.2.

Catalyst	Presence of NaBr	Conversion (%)	-[Enantiomeric Excess] (%).
(a) *MRNi-II	-	100	15
(b) *MRNi-II	In reacting solution	100	17
(c) *MRNi/NaBr-II	In modifying solution	100	81

(11.5ml MAA/0.90g catalyst in 23ml methanol; reaction temperature = 70°C; initial hydrogen pressure = 90 atm).

On comparing the enantiomeric excesses obtained for reactions (a), (b) and (c) it is seen that no enhancement occurred when sodium bromide was added to the reacting solution, as opposed to the modifying solution; neither was there any difference at all in the conversion which was obtained. These results infer that the function of sodium bromide was not one of site blocking, as it would be perfectly possible for bromide ions, when present in the reacting solution, to be adsorbed on to catalytic sites and so there would be no grounds for

expecting any significant differences in the enantioselectivities obtained from reactions (b) and (c). Slight differences could arise since, in (b), bromide ions are being adsorbed from an aqueous solution, whereas, in (c), adsorption would be occurring from a methanolic solution. There may also be some competition between bromide ions and MAA molecules for adsorption, although, since the catalyst is placed in contact with the reacting solution prior to the addition of any hydrogen, bromide ions would not initially be in competition against hydrogen. One further point which should be noted is that the solubility of sodium bromide in methanol was found to be considerably lower than that in water and so the maximum concentration which could be attained in methanol was only about 5%. However, in spite of this, the bromide concentration was sufficiently high for adsorption to occur, if this was how the bromide normally functioned and so it would be expected that the enantioselectivity in reaction (b) would be higher than that observed in (a).

The results in Table 6.7.2 are also inconsistent with those found by Sachtler *et al.*[108] discussed in Section 1.9.3. Sachtler reported that no difference in enantioselectivity was observed when sodium bromide was added to the reacting solution, instead of the modifying solution. However, in the light of Table 6.7.2, it appears highly unlikely that Sachtler's suggestion of a simple coordination process occurring between alkali halide and adsorbed tartrate is correct, since there would be no reason why this process could not occur when the sodium bromide is added to the

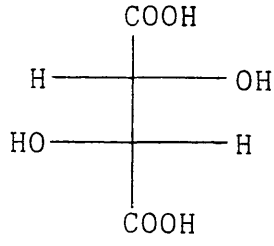
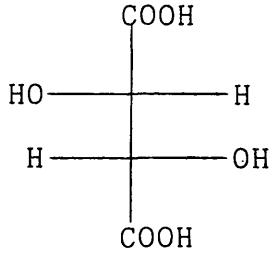
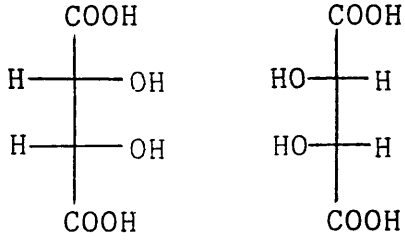
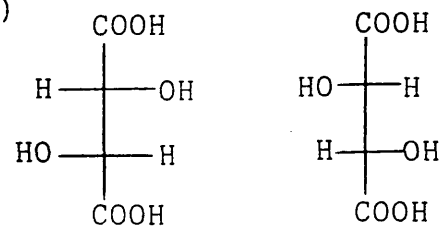
tartaric acid - modified catalyst in the form of a methanolic solution, together with MAA.

The conclusion which can be made is that, in order to obtain maximum enantioselectivity, the sodium bromide must be present in aqueous solution with the tartaric acid during the process of catalyst modification. Some interaction between the alkali halide ions and nickel atoms, or nickel-tartrate complexes, is implied and this is of such a nature that the same interaction cannot take place if the alkali halide is contained in the reacting solution instead of the modifying solution. Sodium ions, however, are brought into contact with the nickel catalyst in the form of aqueous sodium hydroxide on two, separate occasions - first, during the digestion of the Raney alloy and, second, as a result of using sodium hydroxide solution as the means of adjusting the pH of the modifying solution. It might be thought that, since sodium ions are already present within the catalyst system, it must be the bromide ions which are the "active" species within the co-modifier. However, it is pointed out in Section 1.9.3 that highest enantioselectivities were observed when sodium hydroxide was used as the pH adjusting reagent, as opposed to potassium hydroxide, for example.[104] In addition, sodium bromide was found to be a more effective co-modifier than lithium bromide.[71] It therefore appears that the presence of sodium ions in both forms during the process of modification is advantageous. Furthermore, the finding that, of all alkali halides tested, a bromide compound was the most effective suggests that the

presence of bromide ions is also invaluable. Attempts have been made to include compounds such as caesium and lithium bromide in the reacting solution, in an effort to establish whether or not the presence of a cation other than Na^+ had any effect on the behaviour of the bromide ions. Unfortunately, neither dissolved in methanol to any appreciable extent and so the precise action of sodium bromide remains something of a mystery.

Lastly, a careful study has been made of the effect of changing the stereoisomeric form of the tartaric acid modifier and the results are shown in Table 6.7.3.

Table 6.7.3.

Stereoisomeric Form of Tartaric Acid Modifier	Conversion (%)	Enantiomeric Excess (%)
(a)  (R,R)	100	-82
(b)  (S,S)	100	+79
(c)  (R,S) and (S,R)	97	0
(d)  (R,R) and (S,S)	98	0

(11.5ml MAA/0.90g catalyst in 23ml methyl propionate; reaction temperature = 70°C; initial H_2 pressure = 90 atm).

It is seen from Table 6.7.3 that the conversion remained virtually constant, regardless of the stereoisomer of tartaric acid used. The enantiomeric excess underwent a complete reversal on changing the enantiomeric form of the acid from (R,R) to (S,S) - that is, the magnitude of the enantiomeric excess was virtually unchanged, whereas the direction of enantioselectivity was altered from being in favour of (R)-MHB to (S)-MHB. Thus, the results confirm that the direction in which the enantio-differentiating ability of the catalyst operates is controlled by the enantiomeric form of the optically active tartaric acid modifier. In contrast, no enantiomeric excess was observed when either the optically inactive, meso form of the acid or a racemic mixture of optically active, enantiomeric forms of the acid was present in the modifying solution. It is concluded that, in order to obtain a non-zero enantiomeric excess of chiral product in the hydrogenation of MAA, the aqueous solution in which the metal catalyst is modified must itself contain an enantiomeric excess of the chiral agent, which, in this case, was tartaric acid. This point is far from trivial and is discussed further in Chapter 7.

CHAPTER 7

FINAL CONCLUSIONS

During this extensive study of the asymmetric hydrogenation of MAA, the variation of conditions of catalyst modification and reaction have resulted in a drastic improvement in the enantioselectivity achieved during reactions. In addition, valuable information regarding the mechanism of enantioselective hydrogenation has been obtained.

Attention must first be given to the process of adsorption of substrate and modifier. The idea that MAA is adsorbed in its keto form, as opposed to its enol form, seems to have been generally agreed upon.[65,112] In contrast, great controversy exists as to the nature of the adsorbed state of tartaric acid. Whereas α-amino acids are thought to form a chelate complex with a nickel atom, ideas of a similar structure for α-hydroxy acids have been abandoned. Tartaric acid, therefore, is assumed to be adsorbed *via* its acid groups only and the controversy which exists concerns whether one or both carboxylic acid groups are involved. Despite the latter idea being favoured by Hoek and Sachtler[65] and Izumi *et al.*[112], a certain amount of the experimental results presented in Chapter 6 are in opposition to this assumption of a two-site attachment of tartaric acid.

As discussed in Section 6.7, the optimum modifying pH was found to be 3.2 in the case of hydrogenation of MAA at high pressure and it is concluded that the most effective form of the modifier is the monoanion, present as $NaHC_4H_4O_6$. It follows that, with respect to the two carboxylate groups, a non-symmetrical tartrate species is presented to the catalyst

surface and it may be that one type of carboxylate group is adsorbed in preference to the other. In view of Fish and Ollis' findings[67] that surface coverage is maximised when tartaric acid itself is present in the modifying solution, it is likely that, if $NaHC_4H_4O_6$ is indeed adsorbed by one functional group only, the acid group, as opposed to the ($-COO^-Na^+$) group will be involved.

Further evidence, which is in favour of the mono-adsorbed state of tartaric acid, is found in the results shown in Table 6.7.3. If, on the contrary, both carboxylate groups became attached to the catalyst surface it is conceivable that different amounts of steric hindrance would be involved, depending on which particular stereoisomer of tartaric acid was being adsorbed. It would then be possible for the adsorption of one form to be favoured over that of other forms. This would definitely be the case if, as was suggested by Klabunovskii *et al.*[111], enantioselective hydrogenation occurred only on stepped sites on the catalyst. However, the results in Table 6.7.3 do not indicate that this is the case; there is no evidence to suggest that different amounts of acid stereoisomers were adsorbed, since the conversions are almost identical. Furthermore, the zero value of enantiomeric excess obtained for racemic tartaric acid is of particular importance. If the adsorption of, for example, (R,R)-tartaric acid were more favourable than that of the (S,S)-enantiomer, it follows that the former would be adsorbed to a greater extent than the latter. Thus, a small, but distinct

negative enantiomeric excess would be obtained, contrary to the results shown in Table 6.7.3.

It is more likely that adsorption of the modifier occurs *via* one acid group only, leaving the rest of the molecule free to interact with adsorbed MAA. Consequently, the stereoisomeric form of the modifier has no influence on the adsorption process, but, instead, determines whether or not the catalyst possesses any enantio-differentiating ability, and, if so, the direction in which this occurs. The mode of adsorption shown in Figure 1.9.2.8, which was suggested by Izumi *et al.*,[112] is therefore rejected. The idea that adsorption of tartaric acid occurs by one acid group only is consistent with a conclusion reached by Fish and Ollis[67] on the basis of their investigations of the surface coverage of nickel catalysts with tartaric acid by electrochemical techniques; this conclusion was based on the fact that their measurements were consistent with one adsorbed tartaric acid molecule covering 3-3.5 nickel atoms, whereas if tartaric acid were adsorbed by means of both acid groups, an average of nine nickel atoms would be blocked by the adsorption of only one acid molecule. The excellent "template" effect of tartaric acid must arise from the remaining hydroxy and carboxylate groups.

One further point which concerns the adsorbed state of tartaric acid is whether or not corrosive chemisorption occurs. The idea that the attachment of tartrate molecules to a nickel atom results in that atom moving out of

the bulk metal is firmly held by Sachtler[65] and Izumi et al.[113] and, as discussed in Section 6.3, comparable behaviour between heterogeneous modified metal catalysts and homogeneous metal complex catalysts has been found to occur. However, Bostelaar and Sachtler's suggestion[118] of a nickel surface becoming covered with layers of tartrate sheets is rejected on the basis that, in the event of this happening, no explanation as to how unmodified nickel atoms remain available for the purpose of MAA or hydrogen adsorption was provided. In relation to this, Izumi[55] has reported that all Raney nickel catalysts which had previously been modified with tartaric acid displayed some catalytic activity towards the hydrogenation of MAA even when, as was sometimes the case, the enantio-differentiating ability of catalysts was non-existent. Furthermore, Fish and Ollis[67] have found that all electrochemically measured fractional coverages corresponded to a monolayer or less.

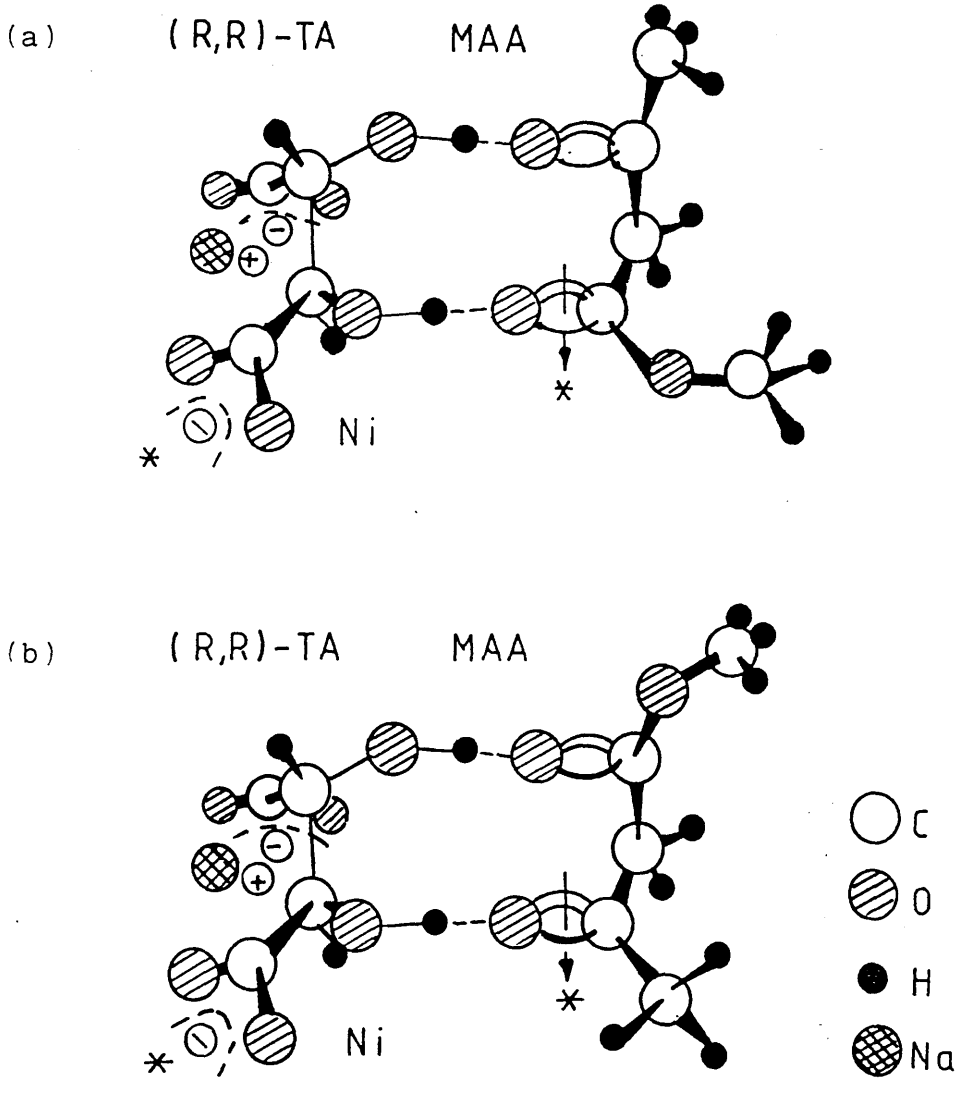
The appearance of a strong green colour was observed when Raney nickel catalysts were modified at a temperature of 100°C and this effect was assigned to the formation of nickel(II) ions by the oxidation of nickel atoms. Since the lowest free energy state of the nickel surface is that of a flat surface, it is expected that the complete removal of nickel atoms as water-soluble complexes of nickel(II) ions will occur from, for example, stepped sites in preference to that of nickel atoms within the flat surfaces which are present. Since an increase in the temperature of modification results in an enhancement in catalyst asymmetric activity, the inference is that the

relatively simple picture of molecules of tartaric acid and MAA adsorbed on nickel atoms, which are contained in a flat nickel surface, is a reasonably accurate representation of the true adsorption processes.

It is generally accepted that the stereochemical mode of interaction between substrate and modifier involves the formation of hydrogen bonds. Since tartaric acid is considered to be adsorbed by one carboxylate group, the possible sites for hydrogen bonding are the remaining carboxylate and two hydroxyl groups. It has been found[57] that the result of substituting one or both hydroxyl groups in some way was a decrease in enantioselectivity and so it is apparent that both groups are involved in the process of stereochemical control. However, the presence of the second acid group within the catalyst modifier was also found to be favourable.[57] If hydrogen bonding is assumed to occur <u>via</u> the two hydroxyl groups, the question which remains is that of the role of this β-COO^- group; this group cannot be completely "free" as the presence of a positive sodium counterion is required to maintain electroneutrality.

MAA can be adsorbed in two different ways with respect to the adsorbed tartrate species and these are shown in Figures 7.1 (a) and (b).

Figure 7.1



Since tartaric acid is not symmetrically adsorbed with respect to its two carboxylate groups, these two adsorption patterns are not equivalent. The exact mechanism of hydrogen insertion is not fully understood and, in the case of Figure 7.1 (a), it is difficult to imagine how hydrogen atoms could gain access to the β-keto group of MAA; one possibility is that some form of transfer mechanism is occurring which involves the adsorbed tartrate species.

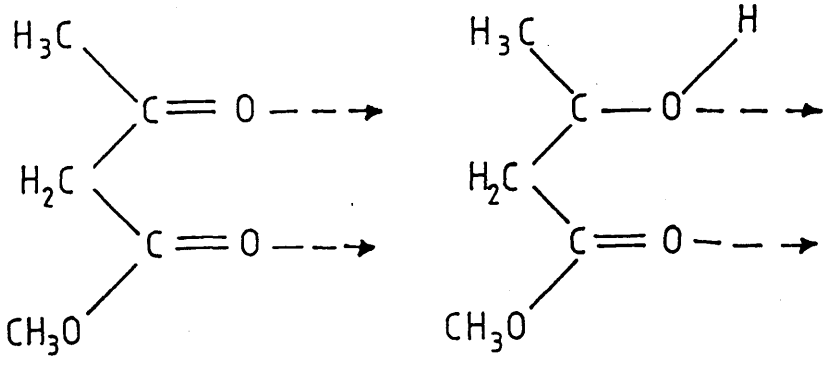
Regardless of the exact mechanism of hydrogenation, if MAA is adsorbed as shown in Figure 7.1 (a) the (S)- enantiomer of MHB would be produced. However, as discussed in Chapter 6, the use of (R,R)-tartaric acid as the modifying agent results in an enantiomeric excess of (R)-MHB in the hydrogenation of MAA and so the adsorption mode shown in Figure 7.1 (a) cannot be that which is favoured. In contrast, (R)-MHB is produced if MAA is adsorbed as shown in Figure 7.1 (b). It is concluded, therefore, that, on the surface of a catalyst modified with (R,R)-tartaric acid, the adsorbed state of MAA which is favoured is that shown in Figure 7.1 (b).

The reduction in enantioselectivity, which has been found to occur in replacing the β-COOH group of tartaric acid with, for example, a $-CH_2OH$ group[56] suggests that the role of the β-COOH group is to regulate the adsorption of MAA so that the resulting structure is that shown in Figure 7.1 (b), as opposed to Figure 7.1 (a); it follows that a β-CH_2OH group does not possess the same ability to determine the adsorption mode of MAA. One major difference between the two functional groups is that sodium ions are present in conjunction with the β-COO^- ions in tartaric acid, whereas no ionic species are present when the β-substituent is a $-CH_2OH$ group. In addition, the significant enhancement in enantioselectivity which occurs on including sodium bromide as a co-modifier must be considered. There is perhaps an overall regulating effect on the adsorption of MAA which is

due to the combined presence of all three types of ionic species; some kind of favourable interaction is apparently occurring between one or more of these species and the $-OCH_3$ group of MAA. This interaction must be strongest when the "foreign" ionic species are Na^+ and Br^-.

The idea that hydrogen bonds exist between adsorbed substrate and modifier complexes is also relevant towards the finding described in Section 6.6 that, under certain reaction conditions, relatively large enantiomeric excesses of MHB were obtained in conjunction with very low conversions of MAA. If MAA is considered to form two hydrogen bonds via its keto and ester carbonyl groups, it follows that, after the hydrogenation reaction has taken place, the product, MHB, is also capable of forming hydrogen bonds in a similar manner. A comparison of the sites available for hydrogen bond formation is shown in Figure 7.2.

Figure 7.2



MAA MHB

(- - → represents site for hydrogen bonding)

Although the actual hydrogenation of MAA may have occurred, it is therefore possible that the adsorbed tartrate complex remains attached to the product in a manner very similar to its original mode of attachment to the substrate.

In addition to its attachment to the catalyst surface, MHB would also be bonded in some way to the adsorbed tartrate complex. In order for MHB to become desorbed from the nickel catalyst, therefore, an additional attractive force must be overcome than would be the case if no neighbouring tartrate complex were present. Consequently, the desorption of MHB from sites with adjacent modifier molecules would be slow - that is, the turnover rate of these catalytic sites would be relatively low.

The idea that enantioselectivity occurs prior to the addition of hydrogen to the substrate is generally accepted without question, however relatively little information is available regarding the actual mechanism of hydrogen insertion. The two theories which are presented in Section 1.9.2 are strikingly different in content and neither can be considered as totally accurate. Hoek and Sachtler's proposal,[65] shown in Figure 1.9.2.4, requires active nickel atoms to become hexa-coordinated during the process of hydrogenation; that is, the nickel is tetra-coordinated with respect to its complex with tartaric acid, which leaves one site available for hydrogen adsorption and one for substrate adsorption. However, this proposal cannot be valid if the nickel atom is to remain attached to the bulk metal structure in some way; this must be the case,

since all "free" metal-modifier complexes would be very effectively removed when the catalyst is washed after the modification step has been carried out. The suggestion that substrate, modifier and hydrogen become adsorbed at the same metal site bears a strong relationship to the mechanism of asymmetric hydrogenation using homogeneous rhodium-diphosphine ligands, although in this latter mechanism, shown in Figure 1.4.3.1, the diphosphine ligand and substrate both behave as bidentate ligands, leaving two sites available for hydrogen addition. The similarity which exists between the hexa-coordinated nickel and rhodium ions clearly shows that a nickel atom (or ion) substituted in this way must be considered as a single molecular entity and not as part of an extended metal structure.

Hoek and Sachtler's proposal[65] of hydrogen spillover occurring from the tartrate ligands to the metal surface is in complete contrast to Izumi's suggestion[113] of the formation of a multilayer of hydrogen, which is shown in Figure 1.9.2.9. However, this latter suggestion provides no basis for any explanation for the occurrence of enantioselective hydrogenation. Although the metal surface is assumed to be saturated with hydrogen, tartaric acid must also be present to some extent, since the modification process is carried out prior to the catalyst being used for reaction purposes; the presence of any adsorbed tartaric acid was not in fact mentioned by Izumi. Thus, tartaric acid is adsorbed at the catalyst surface, whereas Izumi stated that hydrogenation

of MAA must occur at sites distant from the surface - that is, where favourably polarised hydrogen molecules were available. This means that MAA is not hydrogenated in the vicinity of the optically active modifier and so it is impossible to visualise how any enantioselectivity can take place. Izumi's proposal is therefore rejected as being an explanation of the observation of enantioselective hydrogenation.

The reasons for believing that tartaric acid is adsorbed by one -COOH group only have already been presented in this chapter. As a result of this conclusion, there would be no requirement for a nickel atom, active in hydrogenation, to become hexa-coordinated, if Hoek and Sachtler's mechanism[65] is once again considered. Assuming that substrate, modifier and hydrogen become adsorbed on the same nickel atom, each atom would have a maximum of three substituents at any time. However since active nickel atoms are considered to remain in the bulk material to some extent, it is more likely that a sufficiently strong steric interaction will occur if substrate and modifier are adsorbed on different, neighbouring nickel sites, as shown in Figure 7.1.

Hoek and Sachtler gave no explanation as to the mechanism of the suggested hydrogen spillover involving the tartrate ligands. This must involve the replacement of one (or more) hydrogen atoms within the tartrate structure; it is likely that the hydroxyl hydrogen atoms would be involved in preference to those directly bonded to carbon atoms. However, the two hydroxyl groups are hydrogen

bonded to the substrate and so any spillover effect would necessarily disturb this interaction and, therefore, the process of enantioselectivity. Although the theory of hydrogen spillover cannot be discarded, it is difficult to visualise exactly how this transfer of hydrogen could occur. Indeed, this would be a suitable subject for further studies in the area of asymmetric hydrogenation.

During their studies of the effect of co-modifiers Izumi *et al.* suggested that the surface of a modified catalyst consists of two types of catalyst site.[117] However, their claim that the action of sodium bromide is to selectively poison some of the non-enantioselective sites has been disputed by Sachtler *et al.*[118] in favour of the idea that some interaction takes place between modifier and co-modifier. One of the most important features in the general discussion of the role of alkali halide co-modifiers is the validity of the theory that two types of catalyst site exist, where one produces racemic MHB and the other enantiomerically pure MHB. This idea has apparently been universally accepted; for example, it was used as a basis for the simple kinetic model of enantioselectivity proposed by Fish and Ollis[151] in their review on the subject of asymmetric hydrogenation. The alternative view is that any one site can only produce either (R)- or (S)- product and the presence of the modifier enhances one type of site in preference to the other. No comment can be made in favour of either theory in the light of results obtained in this work and it is suggested that this is an area

which also invites further study.

In spite of the doubts which remain over the exact mechanism of heterogeneously catalysed asymmetric hydrogenation reactions, extremely high enantioselectivities in the reduction of prochiral species can be achieved. In this work, successive alterations in the conditions of catalyst modification and reaction have resulted in the hydrogenation of MAA being carried out with an extremely high enantioselectivity. The catalyst with greatest enantio-differentiating ability is modified with an aqueous solution of optically pure tartaric acid and sodium bromide at pH 3.2, with the temperatures of modification and alloy digestion fixed at 100^{o}C. The reaction temperature should be 70^{o}C and the minimum hydrogen pressure which should be used is about 20 atm. Using these conditions, MAA is completely hydrogenated to yield MHB with an enantiomeric excess of magnitude 85% - this figure is representative of an (R):(S) product rate of 92:8. If the mechanism of asymmetric hydrogenation were to be more fully understood, it is highly likely that enantiomeric excesses which are equal to those obtained in homogeneously catalysed reactions, and therefore in biological systems, could be obtained. Consequently, the replacement of homogeneous catalysts with the economically preferred heterogeneous catalysts in the enantioselective hydrogenation of carbonyl - containing compounds, and perhaps even olefinic compounds, may happen in the relatively near future.

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